The Journal of Pediatrics

VOL. 28 JUNE, 1946 NO. 6

Original Communications

THE THICKNESS OF THE SKIN AND SUBCUTANEOUS TISSUE BY AGE AND SEX IN CHILDHOOD

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IT HAS been common practice to note the amount or thickness of the soft tissues overlying certain muscle groups as a part of the routine physical examination of infants and children. The usual procedure has been to select a fold of these tissues in a part which is freely movable, as over the biceps or recti, and assign a rating subjectively, but some physicians have measured this thickness with a ruler, and Franzen[1] devised a special spring caliper to determine it under constant pressure. The thickness of these tissues has received attention as an indication of nutritional state for the obvious reason that the subcutaneous tissue is a repository for the storage of fat and hence reflects any large accumulations or withdrawals of fat in the body. The accumulation or loss of water in this tissue may also account for rapid change in its thickness, but characteristic differences in tissue quality are usually associated with edema or dehydration so that the clinician can recognize when this measurement is grossly distorted by changes in the storage of water.

The subcutaneous tissue varies characteristically in thickness between individuals of different body types, and this variation has much to do with a child's customary position in the weight range and with how closely his weight will approximate the average weight for height and age. The range of difference in this respect between individuals of the same age and in apparent good health is proportionately greater than for most physical attributes. Using Sheldon's[2] classification of body types, a person predominantly endomorphic in type characteristically will have a heavy panniculus adiposus, and hence a thick fold of subcutaneous tissue, whereas an ectomorphic individual will tend to have a light or thin one. These persistent individual characteristics must be taken into account in assessing physical or nutritional status. Associated with differences in physical type undoubtedly are differences in the consumption and utilization of food and in the amount of physical or the rate of physiologic activities, but to some extent these differences may be considered constitutional.

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The studies being reported were made possible during the earlier years by a grant from the General Education Board. During the past three years they have been supported by the James Foundation.

What would represent a normal continuing and satisfactory amount of subcutaneous tissue for one individual might represent gross malnutrition and loss of body substance for another. However, the multiple correlation of five skeletal dimensions with amount of subcutaneous tissue was shown by Franzen[1] to be of a considerably lower order than with amount of muscle, and much lower than with weight. Since weight is primarily a characteristic of body dimensions and can be predicted fairly accurately from a battery of them, and since amount of subcutaneous tissue is much more independent of skeletal dimensions, Franzen concluded that objective determination of the thickness of subcutaneous tissue offers a fuller understanding of nutritional state than does body weight.

Sex and age differences in respect to the thickness of the subcutaneous tissue also have been appreciated to some extent. Franzen called attention to the greater average thickness of this tissue and the greater variability in this respect among girls than among boys of school age. The newborn infant, the preschool child, the young adult, and the elderly person are generally recognized to have less fat in their soft tissues than are the infant 3 to 9 months of age, the adolescent, and the adult of middle age. There are further differences with regard to age in the characteristic locations in which fat is most readily accumulated, but these are of less clinical importance than the recognition of periods of ready accumulation alternating with periods of normal diminution in these stores.

It is clear that valid judgment as to the significance of the amount of skin and subcutaneous tissue in any individual can be made only when age, sex, build, and other contributory factors are taken into account. The evaluation of the thickness of these tissues should continue to receive the attention of physicians in assessing physical status, but this should be done in as objective a manner as possible, and further information is required regarding normal occurrences under the varying conditions referred to.

It is unnecessary to review here the literature on the use and interpretation of direct measurements of skin and subcutaneous tissue because of the excellent studies and discussions of this subject by McCloy[3] published in 1936 and 1938, and the more recent review by Reynolds[4] in connection with studies referred to subsequently. Since McCloy's thorough evaluation of direct measurements, roentgenograms have been used to afford indirect measurements of the soft tissues. Stuart, Hill, and Shaw[5] described a method, applicable to children up to 6 years of age, based upon anteroposterior roentgenograms of the tibial shaft sector of the leg, from which they obtained values for the areas as well as the breadths of the shadows of bone, muscle, and skin and subcutaneous tissues. Norms were presented for these measurements as well as individual case studies. Stuart and Hill[6] in a later publication described a slightly modified technique for use with older children and norms were added for the ages from 6 to 10 years. This method has been used to advantage in several studies of growth and nutrition.[7, 8, 9] Reynolds[4] described a somewhat different technique for using roentgenograms for this purpose, the principal difference being that the film cassette was placed behind the calf of the leg with the child standing, whereas Stuart

and Hill[6] had placed the cassette below the calf with the child recumbent. Reynolds presented norms for actual and relative breadths of the three tissue shadows in the leg for ages from 6½ through 11½ years. His values for breadth of subcutaneous tissue were in very close agreement with those previously published by the other authors.*

In connection with the broader studies of growth and development being conducted by the Department of Maternal and Child Health of the Harvard School of Public Health,[10] the special studies of roentgenograms of the leg have now been carried out on a considerable number of children through their thirteenth birthdays. The two earlier publications dealing with these studies have been referred to,[5, 6] and the techniques used are briefly summarized herewith.† The measurements of the breadth of skin and subcutaneous tissue as obtained in these investigations provide the basis for this report. This measurement, as indicated in the footnote, is the width of the inner and outer shadows cast by the soft tissues overlying the muscles at the greatest breadth of the calf. Although both skin and subcutaneous tissue are included, the term "subcutaneous tissue" will be used henceforth in the text when referring to this measurement.

The measurements of subcutaneous tissue thus derived are presented in Tables I and II for each sex, by age, as percentiles and as means with standard deviations. Certain percentiles are also plotted for the two sexes in Fig. 1. The 50th percentiles in this figure show the marked differences in the average amount of this tissue in infancy as contrasted to childhood, and between girls and boys. The latter difference is slight or questionable in infancy but becomes consistently of more marked degree after two years of age. The 10th and 90th percentiles, including between them 80 per cent of each sex in the series, indicate the extent of variability at different ages.

Fig. 1 shows clearly that the subcutaneous tissue does not increase progressively with age but rather increases and diminishes in cycles, and that girls

*Reynolds studied children of school age and found the standing position satisfactory for the measurement of tissue breadths. The studies of Stuart and his co-workers started with birth, and the recumbent position was essential during infancy. At the age when a child will stand satisfactorily, he will also usually relax when laid on a table, and his leg can then be placed in the proper position without force, and without securing his active cooperation. In following physical attributes throughout the growth period it is often necessary to modify techniques to some extent at different age periods, but it is desirable to have any set of data as comparable as possible at all ages. In the larger project of which the study being reported is a part, the same children have been followed periodically at prescribed age intervals from birth, the oldest children now being 15 years of age. Although both recumbent length and standing height are taken, the former measurement is preferred and used in all case studies. Since use of the recumbent position in taking roentgenograms of the leg has proved satisfactory at all ages, this position has been continued. However, due care must be taken to follow the relatively simple rules prescribed to avoid distortion of shadows.

†The child lies flat on the back with the right leg fully extended at the knee, with the entire leg over the film cassette and with the foot perpendicular to the table. In order to secure complete extension and near parallelism between the leg and the cassette, and the correct position of the foot, it is usually necessary with the infant and often with the young child for an assistant to exert moderate pressure over the lower thigh with one hand while supporting the foot with the other. Forceful pressure over the thigh is avoided in order not to distort the calf by compressing it against the cassette. The older child usually adopts the correct position as directed and requires no holding.

The x-ray tube is centered over the broadest part of the calf at thirty-six inches distance from the film for children up to 6 years of age, and at seventy-two inches for children 6 years and older. The exposure must be such as will allow clear visualization of the outlines of skin, muscle, and bone.

The greatest breadth of calf is determined arbitrarily by measuring the length of the tibial shaft and taking a point three-tenths of this length from the upper end of the shaft. A transverse line drawn through this point was found to give regularly as great a breadth of calf as could be obtained. Total breadth of calf is measured on this line as well as total breadth of muscle. The former measurement minus the latter is the measurement of skin and subcutaneous tissue used in this report, usually referred to simply as subcutaneous tissue.

TABLE I. BREADTH OF SKIN AND SUBCUTANEOUS TISSUE (IN MILLIMETERS) OF BOYS
DISTRIBUTIONS FOR MEASUREMENTS FROM ANTEROPOSTERIOR ROENTGENOGRAMS

AGE (YR.)	PERCENTILES					NO. OF CASES	MEAN	S. D.*
	10	25	50	75	90			
A. Three-Foot Tube Distance								
¼	12	13	15	18	20	66	15	3.3
½	14	17	20	22	24	64	19	3.4
¾	16	18	21	24	26	59	21	4.1
1	15	17	19	22	24	78	19	3.4
1½	14	15	17	19	21	57	17	2.7
2	13	14	16	18	19	74	16	2.8
2½	12	13	14	16	18	66	14	2.3
3	10	12	14	16	18	80	14	2.7
3½	10	12	13	15	17	60	13	2.5
4	10	11	13	14	16	71	13	2.8
4½	10	11	12	14	16	52	12	2.3
5	9	10	12	13	16	71	12	2.6
5½	9	10	11	13	15	54	12	2.6
6	8	10	11	13	16	53	11	3.0
B. Six-Foot Tube Distance								
6	8	10	11	12	14	59	10	2.0
7	8	9	11	12	14	73	10	3.0
8	8	9	11	12	14	64	11	3.0
9	8	8	10	12	14	55	11	3.6
10	8	8	10	12	14	35	10	2.4
11	8	8	12	13	15	25	11	3.1
12	8	9	11	16	19	20	12	3.8
13	8	9	12	16	22	29	14	7.0

*Standard deviation.

TABLE II. BREADTH OF SKIN AND SUBCUTANEOUS TISSUE (IN MILLIMETERS) OF GIRLS
DISTRIBUTIONS FOR MEASUREMENTS FROM ANTEROPOSTERIOR ROENTGENOGRAMS

AGE (YR.)	PERCENTILES					NO. OF CASES	MEAN	S. D.*
	10	25	50	75	90			
A. Three-Foot Tube Distance								
¼	13	15	17	19	20	68	17	2.5
½	16	18	20	22	25	63	19	3.2
¾	17	19	21	23	26	59	21	3.2
1	16	18	20	23	25	74	19	3.2
1½	15	16	17	19	22	60	18	2.8
2	14	15	17	19	21	79	17	2.8
2½	13	15	16	19	21	62	17	2.8
3	13	14	15	18	20	79	16	2.7
3½	12	13	15	17	20	54	15	2.7
4	12	13	15	17	19	72	15	2.6
4½	11	12	14	17	18	60	14	2.7
5	12	13	14	16	18	67	14	2.5
5½	11	12	13	15	17	53	14	2.6
6	11	12	13	15	16	42	14	2.2
B. Six-Foot Tube Distance								
6	10	12	13	16	17	58	13	2.5
7	10	12	13	16	17	63	13	2.8
8	11	12	13	16	18	51	14	2.7
9	11	12	13	16	19	55	14	3.4
10	11	12	14	17	19	42	15	3.5
11	11	12	14	17	19	27	14	3.1
12	13	14	16	18	21	20	16	3.2
13	13	15	17	20	24	19	18	4.2

*Standard deviation.

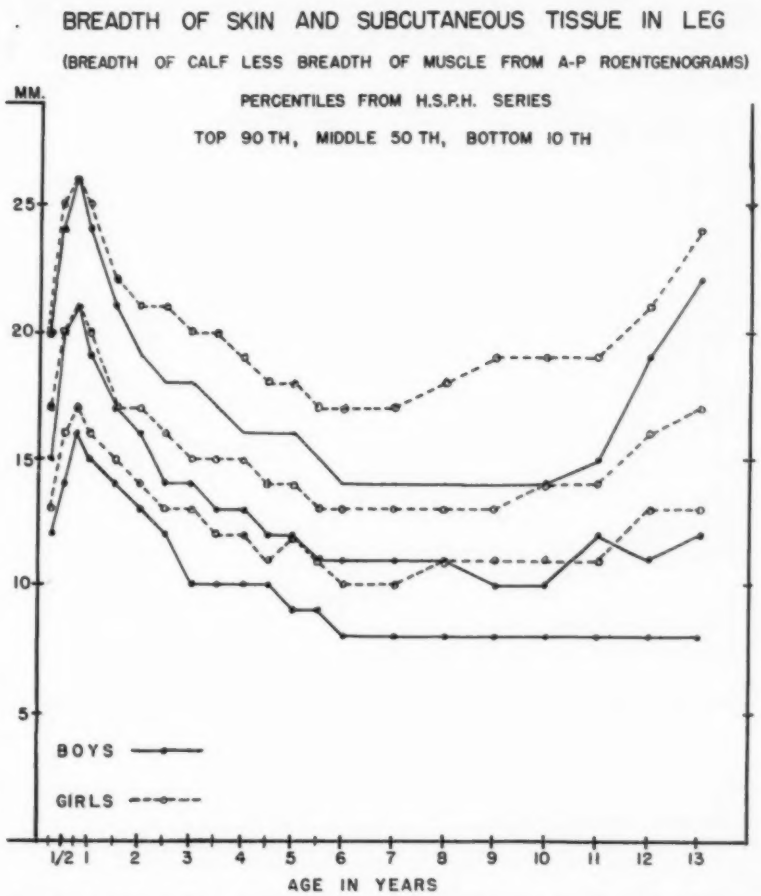
BREADTH OF SKIN AND SUBCUTANEOUS TISSUE IN LEG
(BREADTH OF CALF LESS BREADTH OF MUSCLE FROM A-P ROENTGENOGRAMS)
PERCENTILES FROM H.S.P.H. SERIES
TOP 90 TH, MIDDLE 50 TH, BOTTOM 10 TH
MM.
25
20
15
10
5
BOYS
GIRLS
1/2 1 2 3 4 5 6 7 8 9 10 11 12 13
AGE IN YEARS

Fig. 1.—The graphs in this figure are based upon the norms presented in Tables I and II. They show the characteristic differences in amount of subcutaneous tissue by age and by sex. They also show the wide dispersion of measurements at each age; 10 per cent of each group being excluded above and below the limiting percentiles given.

The curves are not plotted from birth to 3 months and figures are not given for birth in the tables because the roentgenograms taken at that age so frequently showed faulty position. However, the good films indicate that the thickness of subcutaneous tissue at birth is on the average for both sexes about 8.0 mm. Thus, this tissue approximately doubles in thickness during the first three months, and the rise in the graph if plotted would be steeper prior to 3 months than between 3 and 6 months of age.

tend from early childhood to have a thicker panniculus than boys. It shows the necessity for using different criteria in evaluating the physical or nutritional status of boys and girls on the basis of amount of subcutaneous tissue.

Having established a normal expectancy for age and sex in respect to amount of subcutaneous tissue, it is of interest to know how consistent individuals are in following the customary pattern. Can an individual found high or low in the distribution at one age be expected to remain in the same relative position, from year to year throughout childhood, as is customary with skeletal

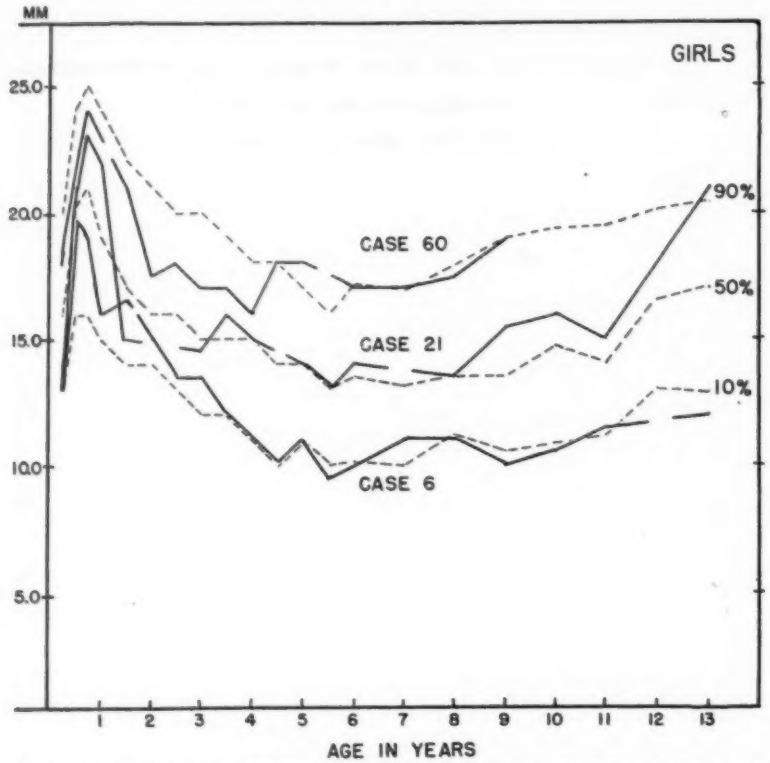

Fig. 2.—This figure shows the curves for amount of skin and subcutaneous tissue of three girls (solid lines) plotted against the 10th, 50th, and 90th percentiles for girls (broken lines). The norms used in this and subsequent figures differ slightly from those presented in F.g. 1 because the latter represents a more recent revision of our data.

Case 6. This girl had a small amount of subcutaneous tissue at all ages but was relatively heavy for herself from 6 months to 2 years. The socioeconomic circumstances of this child's family were continually unfavorable during her childhood, and her position in this distribution may have been influenced thereby.

Case 21. This girl had an average amount of subcutaneous tissue throughout childhood but accumulated excess fat during infancy and adolescence.

Case 60. This girl usually had a thick subcutaneous tissue but became relatively thin for a period from 2 through 4 years of age.

measurements? The data at hand are peculiarly well suited to throw light on this question since so many determinations have been made on the same individuals over such a large portion of the growth period.

Most of the individuals in the series on which these norms are based have conformed to the pattern of change with age as set forth, and, whether fat or thin, have been more or less so at different ages in accordance with this pattern. Fig. 2 shows the curves for three girls, chosen to represent what might be called 10th percentile, 50th percentile, and 90th percentile girls, plotted against the norms for these percentiles. It will be seen that the curves for these individuals follow those for the total series more closely in mid-childhood than they do in infancy or as adolescence approaches. This is in agreement with findings in other aspects of growth, in that the individual tends to be less con-

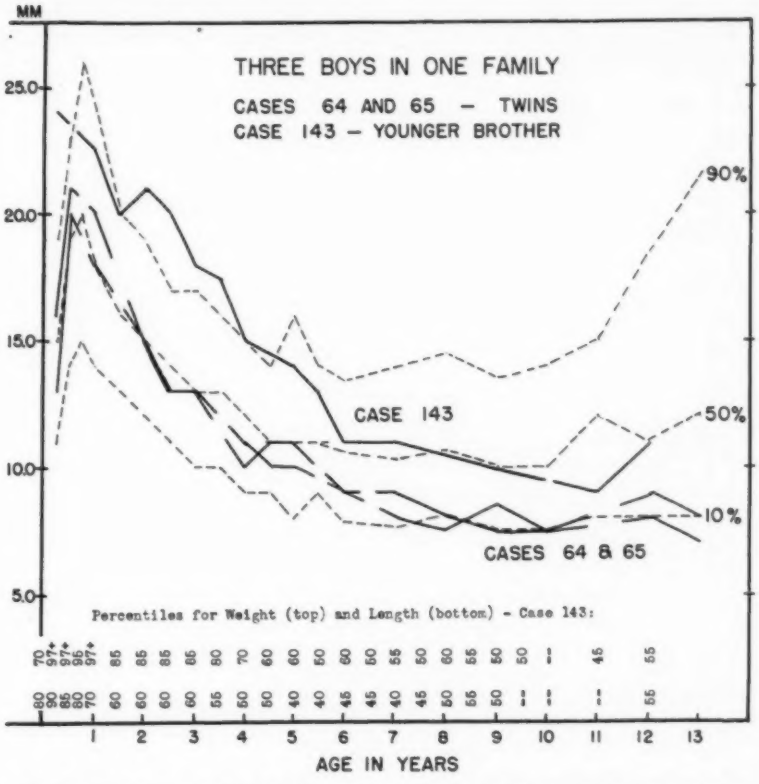

Fig. 3.—The curves of three brothers are presented in this figure because they show a similar change in position respecting the amount of subcutaneous tissue between infancy and six years.

Case 143. This boy showed an extreme amount of this tissue at 3 months of age but had reached an average amount at 6 years and remained average thereafter. His position in the range for length fell somewhat during the former period and his weight during infancy suggests real obesity.

Cases 64 and 65. The older twin brothers of this boy were strikingly alike at all ages and consistently had less subcutaneous tissue than he did. However, the curves of all three children show a similar trend to a lower position in childhood than that held in infancy. Because of this similarity in the behavior of these three brothers, it is assumed that the unusual feature of their growth was dependent upon constitutional or familial factors.

sistent in his position in the range and more readily drifts out of his appropriate channel during the periods of rapid growth than during the intervening period of more moderate growth.

A few children in this series have deviated very markedly from the expected course in respect to the amount of subcutaneous tissue in the calf of the leg at successive ages. In a number of cases there has been a gradual drift from one position in the range to a higher or lower one and the new position has then been maintained at least for a considerable period of time. Satisfactory explanations for these changes have not always been found in the records of food consumption, activity, or illness, and they appear to represent more fundamental variations of individual or family growth patterns. Some of these deflections may be explained, as in other body measurements, by differences between the

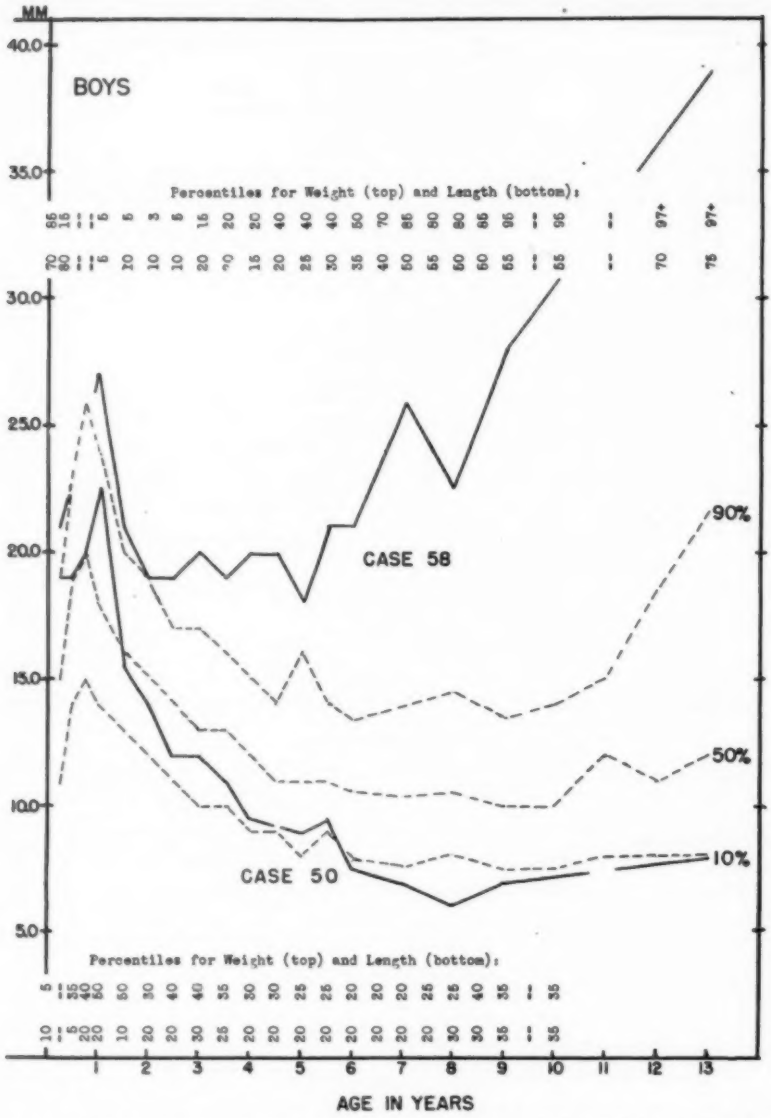

Fig. 4.—This figure presents two contrasting cases in respect to amount of subcutaneous tissue, which did not differ strikingly in this respect until after the first year.

Case 58. This child was temporarily retarded in growth during infancy as shown in the percentiles for height and weight at the top of the figure. This retardation was gradually overcome and he climbed to his initial position for height by his thirteenth year. Concurrently with his retardation he lost subcutaneous tissue and with his acceleration he gained in this respect, but at all ages he was obese and he became extreme in this respect as an older child. At 13 years of age his weight was 6.4 kg. above the 95th percentile. His secondary sex characteristics were developed to an average degree at this age, and his osseous development was never unusual.

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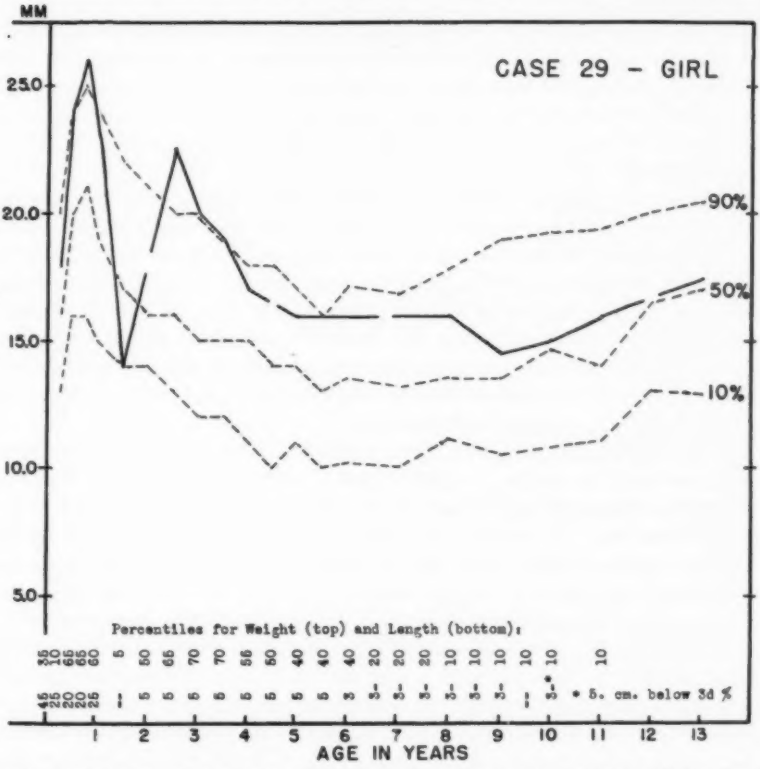

Fig. 5.—*Case 29.* This case is presented because of two abnormalities which were probably to a large extent unrelated. The girl had a short course of celiac disease first recognized at 18 months of age and causing few symptoms after 2 years. In addition, she was stunted in linear growth, principally in the growth of her lower extremities. The retardation was progressive so that at 13 years of age she was by a considerable amount the shortest girl in our series. Her subcutaneous tissue remained ample in amount at all ages except at the time of her celiac disease. Changes in body weight reflected the changes in body size and in amount of soft tissue. Except for the period of restriction while under treatment for celiac disease, this child's diet was considered good up to 5 years of age but only fair or poor for all periods thereafter. The principal deficiencies were in protein and calories.

developmental age and the chronological age of the individual at the time. For example, a girl whose tissue measurement rises steadily between 8 and 10 years of age, when the customary curve is quite flat, may simply be precociously manifesting the rise which commonly accompanies the adolescent acceleration of growth.

In addition to these exceptional trends away from the anticipated course more commonly followed, many children have presented rather marked deviations

(Legend cont'd.)

Case 50. This child was always a more nearly normal individual, being somewhat short but having a satisfactory weight for height and for a short period during infancy being rather heavy, as shown by the percentiles at the bottom of the figure. At 13 years the measurement of the breadth of subcutaneous tissue in Case 58 was 3.9 cm., whereas that in Case 50 was 0.8 cm., a difference of nearly 500 per cent. The dietary histories of these boys did not show differences in customary calorie intakes adequate to explain this finding on a dietary basis. There are many other aspects of the growth and development of Case 58 which are of interest, but outside the scope of this paper. It is planned to present his case more fully in another connection, but his chart is shown here simply as an instance of gross deviation from the normal range for this measurement.

for short periods, remaining at other times in much the same position within the range. Some deviations in the curves are quite clearly exaggerations of normal trends, as, for examples, temporary obesity between 6 and 9 months of age, or excessive loss of soft tissue between 3 and 5 years of age. However, others appear to be related to nutritional factors, disease, or possibly to habits or environment.

Examples of unusual growth patterns, representing some of the types referred to, are presented in Figs. 3, 4, and 5. In the legends to these figures, brief summaries of pertinent clinical data are given to show the most striking relationships, but no attempt has been made to study or present exhaustively all possibly related information available in the records. The purpose here is not to establish the causes for individual variations but merely to call attention to the types which have been recognized. It is proposed, in subsequent reports, to correlate amount of subcutaneous tissue with dietary and other factors and to present more nearly complete case histories.

In the accompanying figures the percentiles for body length and weight by age for a few cases are given in order to show to what extent position in the ranges for these measurements has varied at the times of the unusual trends in the amount of subcutaneous tissue. In a previous publication[5] one of us presented graphs for a number of children which allowed comparisons between the status held and progress made in weight, length, breadth of pelvis, and amounts of bone, muscle, and subcutaneous tissue in the calf. The latter measurements were shown to be of value in revealing the tissue or tissues primarily responsible for unusual weight. In comparing breadth of subcutaneous tissue in the calf of the leg with weight or length, one would not expect the positions for these measurements to be closely alike. Body length would not affect the subcutaneous tissue measurement directly, as it would body weight. Furthermore, general retardation in physical development at the infantile level would lead to short stature, narrow pelvis, and hence relatively light weight, whereas it would tend to keep the breadth of subcutaneous tissue relatively large. However, one would expect to have the latter measurement influence body weight and hence to fluctuate, to a degree, with it. It is for this reason that the measurement of subcutaneous tissue has value in interpreting body weight.

CONCLUSIONS

The thickness of subcutaneous tissue has been shown to increase rapidly up to 9 months of age, then to decrease abruptly and rapidly until 2½ years of age and more slowly until about 5½ years of age. The actual thickness at 5½ years is, on the average, about one-half that at 9 months. Between 5½ and 11 years of age the amount remains unchanged, but between 11 and 13 years of age there is a definite increase which appears to be the beginning of an adolescent accumulation. Two few children have been followed more than thirteen years in this study to plot the average trend beyond that age.

These studies show clearly that girls tend to have more subcutaneous tissue than boys throughout childhood, the 10th percentile for girls being close to the 50th percentile for boys at all ages after 2 years, and at certain ages, surpassing it. These norms do not show any earlier increase in connection with adolescence

among girls than boys as might be expected, but this may be due to the small number of cases included at these older ages.

There is great variability in this measurement between individuals of the same age and sex, especially among infants, and as adolescence approaches. Most children tend to remain in approximately the same part of the range during most of the growth period and to return to it after temporary digressions. They are more inconsistent in this respect in infancy than in childhood. Cases showing various unusual trends have been studied.

Judgments respecting the physical development and nutritional status of children could frequently be improved if the normal variations and trends of amount of subcutaneous tissue were more fully taken into account in interpreting clinical findings and body measurements.

The clinician can recognize differences in the amount of this tissue in different children, but he has difficulty in knowing what significance to attach to them. These must be interpreted in the light of normal occurrences for age, sex, and build, as well as on the basis of history and other clinical findings.

The subjective evaluation of the amount of subcutaneous tissue as customarily determined can serve the experienced physician well in determining status at a single examination. The rating thus given is not usually precise enough to recognize changes between examinations or long-range trends during the growth period.

The principal purpose served by studies of shadows of this tissue in roentgenograms is to contribute to our knowledge of growth in this respect and thereby to improve clinical interpretations. However, the method discussed in this paper can be applied readily by any x-ray technician and might well be used clinically in the study of children exhibiting unusual growth patterns.

It is appreciated that the amount of subcutaneous tisue in the calf may not always reflect the situation in other parts and may be less subject to variation with transitory health and dietary conditions than the looser connective tissues over the upper arm or abdomen. It does appear to be a relatively stable area in which to study persistent individual characteristics or long-range changes.

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A FIFTEEN-YEAR STUDY OF PREMATURITY

From the Standpoint of Incidence, Mortality, and Survival

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THIS is a clinical and statistical survey of premature infants born in the Philadelphia Lying-In, a branch of the Pennsylvania Hospital, encompassing a period of fifteen years beginning Jan. 1, 1930, and ending Dec. 31, 1944. It was in the fall of 1929 that the new maternity building, equipped with nurseries capable of accommodating 125 newborn infants simultaneously, first opened its doors. During the time covered by this investigation, there were 33,668 babies born of which 2,960 were premature, a yearly average of 197. In determining the prematurity of an infant, the regulation issued by the Bureau of Vital Statistics in 1930 was carefully observed. In that year, this regulation stipulated that for any baby of twenty weeks' or more gestation a birth certificate must be furnished and, in case of death, a death certificate. Early in 1943, the ruling was altered, reducing the gestation period to sixteen weeks. This action could be expected to, and did, bring into our statistics an increased number of very small babies that previously had been classified as abortions. The upper limit of prematurity was set at 5½ pounds (2,500 Gm.) which is in conformity with the concepts of the American Academy of Pediatrics. Quite naturally, this upper limit was bound to include full-term babies who were regarded as immature or, as frequently occurred, were of a multiple birth. In collecting the data presented here, these criteria have been faithfully followed. It is obvious that all the details concerning such a large group of premature infants cannot be discussed in one contribution. Some of the more significant and pertinent findings will be given and it is hoped that more will reach publication in the near future.

In assessing the causes of prematurity, there are still a large number of intangible factors which are hard to evaluate properly as to their relative importance. The usual causes have been encountered in this series, such as the presence of a multiple birth, syphilis, toxemia, placental abnormalities, defective maternal genital tracts, acute and/or chronic illness of the mother with termination of pregnancy necessary to preserve her life, emergency surgical procedures that had to be instituted regardless of the baby, and the adherence to the legal requirements of the Bureau of Vital Statistics in determining the gestation period. There were over 400 cases of premature rupture of the membranes, about one-fifth being accounted for by accidents to the mother, but no adequate explanation could be found for the other four-fifths. Most of our previable babies made up a group for which no reason could be discovered

Grateful acknowledgment is made to the Mead-Johnson Pediatric Research Fund, established at the Pennsylvania Hospital in 1940, for making it possible to compile the statistics necessary for this paper.

to explain why they were not carried to term. In the early years of this study, it was difficult to secure the interest of the obstetric staff in any attempt to determine the etiology in these cases, but as time progressed and we were able to prove that our greatest mortality occurred under such circumstances, our records improved.

The pursuant data on the incidence of prematurity, factors influencing mortality, and pertinent observations on the survival of premature infants will be discussed.

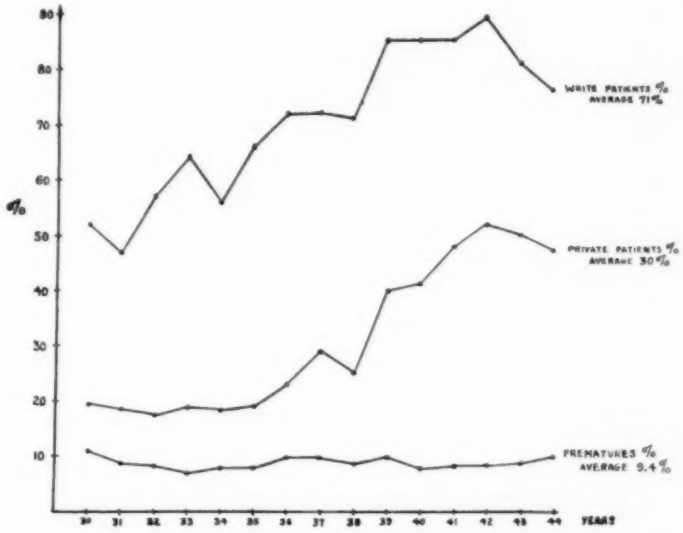

Chart 1.—The incidence of prematurity.

INCIDENCE OF PREMATURITY

In studying the occurrence of premature babies in the fifteen years of this report, only a slight annual fluctuation was noted during the entire period of time. It appears that all our efforts to bring about a reduction in premature births have been fruitless, but a number of significant facts have been uncovered that are worthy of recording, particularly the one of dietary control initiated in 1932. Chart 1 establishes the fact that the average per cent of premature infants was 9.4, with the highest incidence of 10.2 occurring in 1930, and the lowest of 7.5 in 1933. On the same chart may be noted the decided increase in the percentage of private patients from 19.6 in 1930, to 47.4 in 1944. As the personnel of the obstetric staff increased, there was a concomitant acquisition of more private patients through this circumstance and the hospital devoted more of its facilities, from then on, to caring for a responsible group of women, with less space being available for charity cases. As a result, during the fifteen years, 30 per cent of all premature babies were private patients and these babies, with few exceptions, were given prenatal care and delivered by

recognized obstetricians. The ward patients were attended by residents and interns. Chart 1 shows also a marked increase in the number of white patients, from 52 per cent in 1930, to 71 per cent in 1944, and during the years 1939, 1940, 1941, and 1942, they constituted well over 80 per cent of all cases. The average of white patients among our premature infants for the entire period was 71 per cent. Despite this situation, which developed gradually through the years, there was no obvious favorable response in the number of premature deliveries.

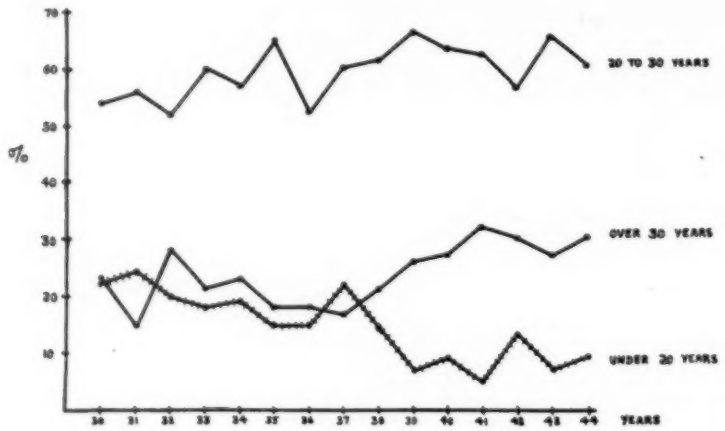

Chart 2.—The age of the mother.

Age of the Mother.—The influence this factor plays in the production of prematurity has been commented upon in medical literature, but too few cases have been included and the surveys have not been continued over a long enough period of time to be conclusive. In order to reflect the comparative ages of the mothers of our premature babies, they were divided into three groups (Chart 2) and it was discovered that the greatest incidence appeared in mothers between 20 and 30 years of age, constituting 59 per cent of the cases over the entire period covered by this survey. There was found also a tendency for the number of premature infants to increase in this age group during the fifteen years, while mothers under 20 years of age, comprising about 20 per cent at the beginning of this study, less frequently failed to reach full term from 1937 on, averaging only 10 per cent. At the same time more mothers over 30 years of age were delivered after 1937, an increase from about 20 to over 30 per cent. It is noteworthy that more mothers over 30 years of age participated in both full-term and premature births. The decline in the number of mothers under 20 years can be ascribed to the fewer Negro patients who, in the early years, constituted a considerable group of very young, unmarried, and immature girls. This shifting of age groups from the poorer class of women to the more stable and economically solvent ones does not seem to have influenced the course of events.

Prenatal Care.—So many changes have taken place in the details of prenatal care in our institution during the time covered by this survey that the only common denominator remaining for the purpose of this paper is the number of prenatal visits made by each patient. The minimum deemed necessary for satisfactory care has been arbitrarily set at four per patient, but at the same time it is recognized that without understanding and skillful medical attention and the cooperation of the mother, the number of prenatal visits assumes less importance. In 1930, only 40 per cent of the pregnant women fulfilled these minimum requirements, but, in 1944, well over 90 per cent had cooperated, most of them receiving as much care as was considered adequate. Not only was improvement noted in attendance for routine examinations, but a diligent effort was made to stress diet and vitamins as an important part of prenatal care.

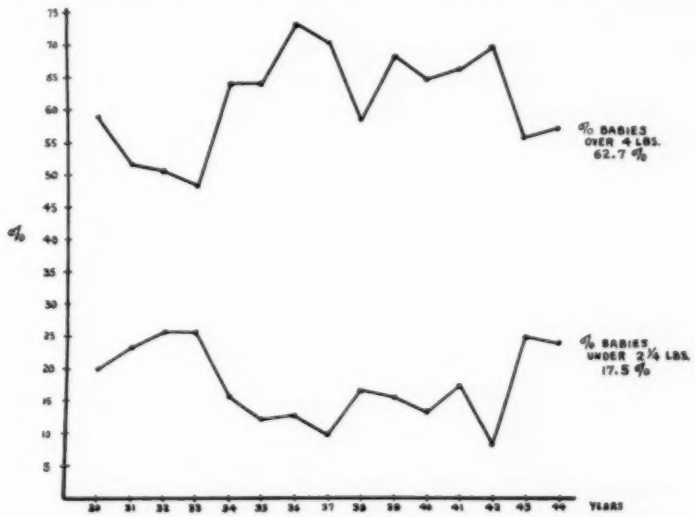

Chart 3.—The incidence of big and small premature babies.

To what extent it succeeded is shown in Chart 3. In November, 1932, a motion was passed by the Staff recommending that a diet containing greater amounts of vitamins, proteins, and minerals be insisted upon for all patients during their prenatal course. While it was not a well-controlled effort and had no obvious effect on the number of premature infants, it apparently had a definite influence on the occurrence of increasing numbers of big premature infants (over 4 pounds) and of decreasing numbers of previable babies under 2¼ pounds (1,000 Gm.). This was consistently true with the exception of the period of time when the term of gestation was reduced from twenty weeks to sixteen weeks in May, 1943. However, one of our staff obstetricians was able to effectively demonstrate the value of a scientifically controlled diet during pregnancy. A group of 750 expectant mothers was given a special diet containing large amounts of proteins, vitamins, and minerals with definite limitation

of fluids and water-embracing fruits.[1] Adequate supervision was secured by having one physician examine all patients, one nurse make all home visits, and the hospital issue all dietary instructions. Not one case of prematurity occurred in this group, while there were 37 cases in a similar group not on the special diet.

MORTALITY

Of the many factors influencing the mortality of premature infants, there are several outstanding ones which are of immediate importance. It must be understood that this report applies only to the time during which the patient remained in the maternity hospital and that a good many of the large premature infants were allowed to go home after two weeks, provided their weight was above 5 pounds and they were established on a satisfactory feeding schedule. However, most of these infants remained for an extended period of time, often for as long as three months. The mortality of this series of 2,960 cases has been analyzed from the following standpoints: relationship to total infant mortality, stillbirths and neonatal deaths, length of life, birth weight, sex, age of mother, multiple births, emergencies, syphilis, toxemia, cord and/or placental complications, and methods of delivery.

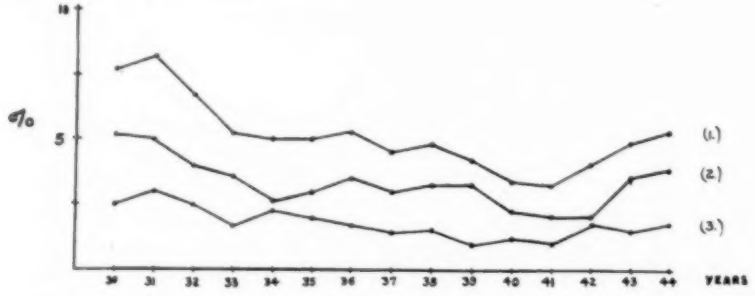

Chart 4.—Mortality. *1*, total deaths 5.1 per cent. *2*, premature deaths 3.3 per cent. *3*, full-term deaths 1.8 per cent.

For purposes of comparison, data on full-term and premature mortality, based on 33,668 babies delivered during the fifteen-year period, are given in Chart 4. There were 600 full-term babies among the 1,740 infant deaths, averaging 1.8 per cent of the total, with the highest mortality (3.2 per cent) occurring in 1931, and the lowest (1 per cent) in 1941. The remaining 1,140 deaths were of premature infants, averaging 3.3 per cent of the total with the greatest number of deaths (5.2 per cent) taking place in 1930, and the lowest (2 per cent) in 1942. The total mortality of the entire group, comprising 30,708 full-term babies and 2,960 premature ones, was 5.1 per cent.

Of the 2,960 premature infants born during this time, 1,140 (38.5 per cent) died. The yearly fluctuation is shown in Chart 5. The highest premature infant mortality (56 per cent) occurred in 1931, and the lowest (26 per cent) in 1940 and 1941. For the seven years from 1934 to 1941, our premature infant mortality was under 35 per cent. There is no question of doubt that the birth

weight of premature infants is an important factor in their survival. As the number of big babies (over 4 pounds) increased in 1934, and the number of previable babies (under 2¼ pounds) decreased that same year, the total mortality among our premature infants dropped decidedly. The greatest influx of previable infants occurred in 1944, there being 50 such cases with 27 under 1 pound in weight. As a matter of interest, there were 182 babies, 1 pound in

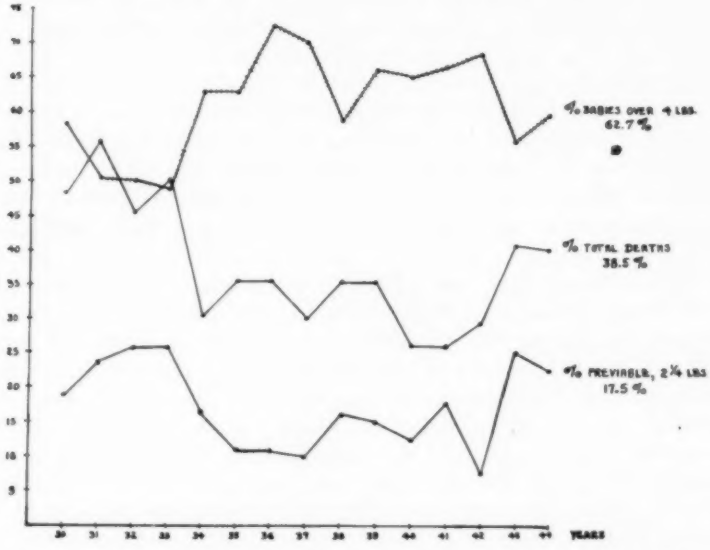

Chart 5.—Relation of deaths to percentages of previable and of big babies.

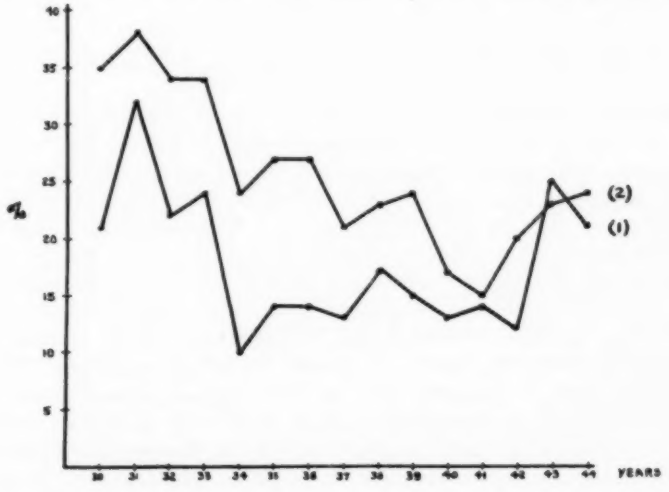

Chart 6.—Yearly fluctuations. *1*, stillbirths. *2*, neonatal deaths.

weight or under, born during the fifteen years and they are included in this report. The mortality rate also increased suddenly in 1943, when there was a decided preponderance of small babies with a corresponding diminution in the number of large ones. However, the lower mortality rate of between 30 and 35 per cent remained at that level due to the fact that the incidence of large and small babies was reasonably constant from 1934 to 1942. Again it seems apparent that the latest ruling of the Bureau of Vital Statistics (sixteen weeks' gestation period) has been at least partially responsible for these facts. On the other hand, we must consider the part World War II has played, introducing emotional strain into the daily lives of ordinarily calm women, as well as financial instability, and the appalling though understandable tendency to travel all over the country under adverse conditions in order to be with their husbands.

In classifying the 1,140 premature infant deaths, there were found to be 522 stillbirths and 618 neonatal deaths (Chart 6). Any baby who had no heart beat at birth, who made no voluntary respiratory effort, and who demonstrated no muscular movements was classified as a stillbirth. The presence of any one of these reactions immediately placed the child in the category of a neonatal death. Stillborn infants made up 17.6 per cent of the total premature births, the greatest number (32 per cent) occurring in 1931, and the lowest (15 per cent) in 1934. Of the 618 neonatal deaths, 501 infants died in the first forty-eight hours, 164 dying in the delivery room (living from five to sixty minutes), making the mortality in the first forty-eight hours 20.8 per cent, based on 2,438 premature infants born alive. Also 81 per cent (501) of our 618 neonatal deaths were in the first forty-eight hours and 19 per cent afterward. If the 164 babies who died in the delivery room are excluded from the total number of living premature babies, then only 2,274 premature infants were admitted to the nurseries. On that basis, the mortality of the first forty-eight hours is 14.8 per cent and the mortality after this time is 4.8 per cent. Of the 501 premature infants unable to survive the first forty-eight hours, 458 (74 per cent) died during the first twenty-four hours of life, and 43 (7 per cent) in the second twenty-four hours.

Babies who are born dead and those who die within the first two days of life die, in most instances, as the result of complications of pregnancy, labor, and delivery. The responsibility for such deaths cannot always be attributed to one definite factor but is usually a combination of more than one. It appears from our experience that heroic efforts exerted under these conditions will save only a few babies. One wonders whether the reason for this can be attributed to failure of our technique or whether it is the result of what has existed before and during birth. The babies who die after the second day allow the pediatrician sufficient time for clinical observation and laboratory study, enabling him to more certainly assign the death to a specific pathologic condition. There were 117 premature deaths occurring after the first forty-eight hours, and autopsies in 60 cases revealed the immediate causes of death to be as follows: pneumonia, 31; malformations, 10; diarrhea, 3; hemorrhagic disease, 2; erythroblastosis fetalis, 1; meningitis, 2; septicemia, 2; prematurity, 29; unknown, 12; and intracranial hemorrhage, 6 (delivery complication). Systemic and pathologic con-

ditions of the mother which made survival extremely unlikely included placental and/or cord anomalies, 4; toxemia, 4; syphilis, 7; and other diseases or illness, 4.

Sex.—Contrary to what has frequently been reported, our records reveal that there were more female than male premature infants and that the mortality was higher in the males by more than 8 per cent. There were 1,418 male premature babies of whom 608 (42.8 per cent) died and 1,542 female infants of whom 532 (34.5 per cent) succumbed. The relative numbers of premature infants of both sexes were fairly uniform throughout the period, as were the deaths.

TABLE I. AGE OF MOTHER IN RELATION TO MORTALITY OF PREMATURE INFANTS

	TOTAL CASES (%)	TOTAL MORTALITY (%)	GROUP MORTALITY (%)
20 to 30 yr.	59	53	34
Under 20 yr.	16	15	35
Over 30 yr.	25	31	50

Age of the Mother.—It has been shown previously (Chart 1) and also in Table I that 59 per cent of our premature infants were born to mothers between the ages of 20 and 30 years, accounting for 53 per cent of our total infant deaths, while the mortality rate in this group alone was only 34 per cent. Mothers under 20 years of age, comprising 16 per cent of the premature deliveries, accounted for 15 per cent of the total infant deaths with a mortality of 35 per cent. Mothers over 30 years of age gave birth to 25 per cent of the premature babies, accounting for 31 per cent of all the premature deaths, but the mortality in this group was 50 per cent. It would appear from these statistics that premature babies born to mothers over 30 years of age are less viable and do not have the ability to survive which is more apparent in those babies born prematurely to mothers of younger age. The reason underlying this observation is obscure.

Multiple Births.—Infants, premature as a result of a multiple birth, have a lower mortality percentage than do single premature infants.[2] Twins are more likely to be a little larger, less immature, and closer to full term than single premature infants. In our group, there were 169 sets of twins, both babies included, and there also were 57 siblings of twins, the other twin being above our upper weight limit and, therefore, not included. There were two sets of triplets (all of one set died) and one set of quadruplets. Among our premature births, there were 405 babies of multiple births of whom 127 (31 per cent) died. In Table II is shown the mortality of first- and second-born twins

TABLE II. MORTALITY OF FIRST AND SECOND TWIN

First twin	
Under 3 pounds	89%
Over 3 pounds	11%
Total	29.5%
Second twin	
Under 3 pounds	95%
Over 3 pounds	16%
Total	33%

according to whether they were under or over 3 pounds birth weight. Twenty-two per cent of the twins were under and 78 per cent over 3 pounds. It appears more dangerous to be the second of twins.

Emergency Cases.—During the fifteen years of this survey, there were 381 (12.8 per cent) unregistered emergency cases and of this number, 245 (64 per cent) died. In 1930, almost 40 per cent of our total premature births belonged in this category, while in 1944, only 6.8 per cent did. As the hospital developed and began to accept more private patients, accommodating fewer Negro patients, the number of emergency deliveries decreased. Another contributing factor was the definitely improved attitude of all patients, particularly in their cooperation with regard to prenatal care, but in spite of these changes the mortality rate of this group of cases remained constantly high throughout the entire time.

Syphilis.—Positive Wassermann reactions were found in 207 (7 per cent) of the mothers. From 1930 to 1935, there were 116 such cases and only 91 in the following ten years. This improvement was due in large measure to the elimination of uncooperative Negro mothers but directly was the result of intensive syphilitic chemotherapy in recent years.

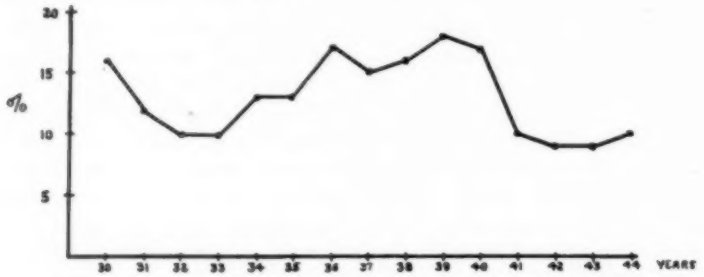

Chart 7.—Incidence percentage of toxemia among mothers of premature babies.

Toxemia.—The relationship of toxemia of pregnancy to the mortality of premature infants has provoked considerable discussion. In this study, there have been 386 such cases with 143 (37 per cent) deaths, although its occurrence has fluctuated somewhat during the fifteen-year period. The highest incidence occurred in 1939 with 18 per cent, and the lowest in 1942 and 1943 with 9 per cent (Chart 7). The fluctuation is shown on the graph. These were well-defined cases and did not include the many others of ankle edema.

TABLE III. TOXEMIA

	CASES (%)	DEATHS (%)	COMPLICATIONS (%)
Group I (over 4 pounds)	61	21.5	77.7
Group II (3-4 pounds)	19	45.7	60.0
Group III (under 3 pounds)	20	75.0	39.0

In order to illustrate the relationship between toxemia of pregnancy, complications, and birth weight of premature babies, the 386 cases have been di-

vided into three groups (Table III) of which 143 died, and 82 of these deaths were accompanied by complications. The complications encountered included syphilis, cord and/or placental conditions, accidents of delivery, and processes in the child inimical to life. Group I, made up of babies weighing over 4 pounds, has the most cases but, at the same time, it has the lowest percentage of deaths and the highest percentage of complications in those deaths, the complications being the most important item in the mortality. In Group II, the size of the baby and the complications encountered in the fatal cases were of about equal importance as causes of inability to survive, while Group III had the lowest number of complications in the fatal cases and the highest percentage of deaths. It can be stated that Group III is a most dramatic reminder of how important the size of the baby is in its fight for life and it would appear to be more important than toxemia itself.

Cord and Placental Complications.—The complications of pregnancy, labor, and delivery may represent danger to the mother, but they are always far more dangerous to the infant. Conditions affecting the cord, such as prolapse, knots, twists, malformations, or loops about a part of the body, must be dealt with promptly, generally by some form of operative obstetric procedure. Placental abnormalities such as placenta previa, premature separation, fibrosis, calcification, infarction, and necrosis are all dangerous to the life of the child. In Table IV is shown the number of such cases together with the number of stillbirths and neonatal deaths. When these particular types of complications are considered from the standpoint of the birth weight of the child, it is found that of the 436 babies, 146, or 33 per cent, weighed under 3 pounds and the mortality rate was 94 per cent. There were 141 deaths in this weight group and 123 of them were definitely related to the coexisting complication. Of the entire 436 babies, 290 (66 per cent) weighed over 3 pounds and 134 (46 per cent) died. In 115 of these deaths, there was a definite relationship between the death and the specific complication.

TABLE IV. INFLUENCE OF CORD AND PLACENTAL CONDITIONS

	TOTAL CASES	LIVING	STILL-BIRTHS	NEONATAL DEATHS	TOTAL DEATHS	% OF DEATHS
Cord	140	67	49	24	73	52
Placenta previa	73	28	11	34	45	61
Placental separation	140	45	50	45	95	68
Placental defects	83	19	48	16	64	77
Totals	436	157	158	119	277	63

In considering the role of these pathologic contingencies of pregnancy with regard to the prematurity mortality, the ratio between babies over 3 pounds and under 3 pounds is 2 to 1. From the same standpoint, the ratio in cord complications is 3 to 1; in placenta previa, 2 to 1; and in placental separation and placental defects combined, 3 to 2. Since the proportion of small babies (under 3 pounds) is greater in placental than in cord complications, the mortality can also be expected to be higher. When the 140 cases of placental separation and the 83 cases of placental defects are combined, we find that they comprise 51 per cent of the total babies in this group and 58 per cent of the fatal-

ities. It is interesting to note that neonatal deaths are greater in placenta previa cases while stillbirths are higher in cord abnormalities, placental separation, and placental defect cases. In view of these facts, it is evident that birth weight is a matter for deep consideration when coupled with cord and placental complications, apparently being the reason for the high mortality in placental separation and defects. However, there is no question about the seriousness of cord and placental complications of pregnancy and, while birth weight is influential, the extent of the complication, and the time element involved between the onset of the condition, the moment it is diagnosed, and the appropriate action taken, are far more important. The mortality of this portion of our prematurity cases is 63 per cent. In relation to the 2,534 babies who did not experience these difficulties, the mortality is only 34 per cent but the ratio of babies over, to those under, 3 pounds is 4 to 1.

The cause of death in many of these babies can be ascribed to asphyxia. The clinical course followed by them consisted of repeated cyanotic attacks, listlessness, inactivity, poor feeding ability, temperature fluctuations, and convulsive symptoms. The autopsy findings showed generalized congestion, petechial and massive hemorrhages in various organs, and considerable edema of the brain.

TABLE V. METHOD OF DELIVERY IN RELATION TO PREMATURE MORTALITY

METHOD OF DELIVERY	CASES	TOTAL DELIVERIES (%)	UNDER 3 POUNDS	COMPLICATIONS	DEATHS (%)
Spontaneous vertex	1238	41	37	42	50
Forceps on vertex	921	31	3	28	11
Breech	411	13	42	42	60
Version	121	4	15	30	35
Cesarean section	269	9	19	94	40

Method of Delivery.—The implication in numerous articles regarding the relationship between the method used to deliver premature babies and their mortality[3] appears to be erroneous after considering Table V. Here there has been no selection of cases for any reason whatsoever, either favorable or unfavorable to any particular method of delivery. The figures given constitute an over-all picture of the relationship between mortality (both stillbirths and neonatal deaths) and delivery methods in this series of 2,960 premature births. It would seem that there are factors more important than the type of delivery employed. It would be most unwise to consider alone the fact that 50 per cent of the infants born by spontaneous vertex presentation (comprising 41 per cent of the total premature deliveries) had died, without also considering the fact that 37 per cent of these babies weighed less than 3 pounds at birth. At the same time, it was in this group that the greatest number of emergencies without prenatal care existed—babies born on the way to the hospital or immediately after admission. An appreciable number of them were known to be dead babies and the method of delivery selected was the best one for the safety of the mother. Of primary importance were the complicating factors in both mother and child which brought about the premature birth, such as syphilis, toxemia, placental and cord conditions, accidents, and other systemic diseases of the mother in-

compatible with a full-term pregnancy, as well as intracranial hemorrhage, pneumonia, malformations, and Rh incompatibility on the part of the baby. There were also a number of habitual aborters and women who had in the past given birth to premature infants.

Forceps applied to the vertex constituted 31 per cent of the total with a mortality of only 11 per cent. Superficially, these percentages could be interpreted as signifying that this is a safer way to deliver a premature infant, but when other information is examined, a different viewpoint is obtained, for only 3 per cent of these babies weighed under 3 pounds and there were maternal or fetal complications in but 28 per cent of the cases. The difficulties encountered in this group were definitely less severe and of less importance than those occurring in the spontaneous vertex deliveries. It is of interest to note that there has been a consistent increase in the number of forceps deliveries, corresponding somewhat with the more frequent occurrence of large premature babies weighing over 4 pounds.

The highest mortality among our premature infants took place in breech deliveries. Of the 13 per cent breech deliveries, 60 per cent did not survive. There was very little variation in the number of premature infants delivered by this method throughout the fifteen-year period, and it is significant that 42 per cent of them weighed under 3 pounds, which is a decidedly high incidence of small babies. The maternal and fetal complicating factors in this group averaged 42 per cent and also were of the more dangerous type. It can be stated with safety that breech delivery is the most hazardous of ordeals for the premature infant.

Versions comprised 4 per cent of the total premature deliveries with a mortality of 35 per cent, being employed in three-fifths of the cases in delivering the second of twins. A number of these were elective versions for reasons other than multiple birth. Only 15 per cent of the babies were under 3 pounds birth weight and 30 per cent were accompanied by anomalies, the most serious one being the malposition of the baby. Other than the existence of a multiple birth, the difficulties attending this type of delivery were not too severe in character and the method has been used with decreasing frequency. It has the second lowest mortality and second lowest number of complications. It might be well to give this method of delivery more attention.

The advisability of performing a cesarean section to deliver premature babies has always been a hotly disputed problem. Nine per cent of our patients were delivered in this manner with a resulting mortality of 40 per cent which, on the surface, appears highly significant. However, when we realize that 19 per cent of the babies weighed under 3 pounds and that 94 per cent were attended by maternal complications demanding immediate intervention, the picture assumes an entirely different perspective. Most of these were emergencies where some action was needed promptly, not only for the survival of the child but, in many instances, to preserve the life of the mother. As is always the case in situations of this kind, the additional danger of shock to the baby was encountered, caused not only by hemorrhage and the rather deep anesthesia necessary for such an operative procedure, but particularly attributable to the time

element involved from the onset of the acute symptoms to the point at which the baby was born, the extent of anoxemia, and the depth of respirations. There is no question of doubt that more cesarean sections are being performed. In the first five years of this survey, only 6 per cent of the premature infants were delivered in this manner, but in the last ten years the incidence has risen to 10 per cent.

For means of comparison, in view of these remarks on the relative merits of different methods of delivery, a rather rough survey of fetal mortality was made in over 24,000 births of full-term infants whose birth weights were over 2,500 Gm. (5½ pounds) with the following results: vertex 2.1 per cent, forceps 1.4 per cent, breech 7.6 per cent, version 3.8 per cent, and cesarean section 4.1 per cent. A complete survey will be given when the deaths of full-term infants are analyzed.

SURVIVAL OF PREMATURE INFANTS

The chances for survival of a premature infant depend more on what occurs before and during delivery than it does on what happens afterward. Of the many factors influencing their ability to live, the outstanding one is birth weight. The nearer to full-term the child is carried and the greater the birth weight, the better is the prognosis. Of the 2,960 premature babies under consideration, 1,820 were discharged from the hospital. A few were discharged against advice and are known to have succumbed shortly after, either at home or in another hospital. In Table VI, they are classified according to their weight in pounds.

TABLE VI

WEIGHT	TOTAL	PER CENT OF TOTAL PREMATURES	PER CENT OF SURVIVAL
Under 2 pounds	384	12.9	2
2 to 3 pounds	331	11.1	20
3 to 4 pounds	414	13.9	46
4 to 5 pounds	848	28.6	81
5 to 5½ pounds	982	33.1	91

In the early years of this report, we were constantly asking ourselves why a premature infant did not survive when no obvious answer could be found to explain it in either the prenatal or natal period. The absence of conclusive clinical evidence or of autopsy findings increased our wonderment. Blame was placed on anatomic and physiologic failures[4] in the child, referring particularly to the location of blood vessels in the lungs, whether or not they were too far away from the air vesicles. Others have reported similar findings about the medulla.[5, 6] Full appreciation of the destructive effects of anoxemia has been slow in coming to our consciousness.

Feeding.—A vital part of our struggle to maintain life in premature babies is concerned with how to feed them. Individual workers in this specialized field have developed effective techniques with various types of milk but it is our belief that a great deal depends on the skill of the pediatrician in manipulating the food in each particular case. Results can be identical, regardless of the food used. Our plan of action has been to withhold all milk feedings during

the first twelve to twenty-four hours, during which time small amounts of boiled water, either with or without sugar, have been offered. It has been our custom to begin with food of low caloric value, gradually increasing it, but seldom exceeding 60 calories per pound body of weight per day, the first consideration being the establishment of good digestion rather than gain in weight. When there is no vomiting or abdominal distention and there are perfectly normal stools, we believe it possible to go ahead with confidence that the gastrointestinal tract is functioning effectively. This is usually accomplished sometime between the seventh and fourteenth days of life and at that time vitamins may be added to the regime. Our choice of food for premature infants has been breast milk, regardless of its supposed deficiency and our faith has been justified, for it has met all the necessary requirements. In one of our numerous attempts to appraise clinically the relative values of foods for premature infants, breast milk, lactic acid certified milk of varying fat percentages, and two dried milk preparations were given to four groups of premature babies whose birth weights were about 4 pounds. While the average daily gain on breast milk was slightly less than on the others, it was the consensus of opinion that the babies were more comfortable on it.[7]

The hours of feeding have varied depending more upon the size and capacity of the child than upon a preconceived nursery regulation. Most of the small babies are fed every two hours, with twelve feedings daily. Changes in the schedule are made in each case to meet the needs of the infant, aiming at a four-hour feeding regime with five to six feedings per day. The two-hour feeding for very small premature infants has been instituted to allow as much fluid as possible by mouth in order to avoid parenteral administration of other fluids, the amounts given at the beginning varying between one-eighth to one-half ounce. As a rule, any increase in the original amount is left to the discretion of the nurse in charge, who is required to confine her activities in this respect within the limitations set by the pediatrician. She is given authority to either reduce or increase the amount at any feeding, the amount depending upon conditions.

The method of feeding is adapted to the individual case, but practically all small infants are fed by gavage because of their poor sucking and swallowing reactions as well as to conserve their energy. In addition, less time is consumed by this procedure. As soon as it is indicated by the condition of the baby, a trial is made with a Breck feeder or a bottle with a small, soft nipple with holes of adequate size, always bearing in mind that the method selected should be the one best suited to the individual child. It is often necessary to proceed cautiously with increases for two weeks before sufficient food can be offered to secure any gain in weight, but by exercising care digestive disturbances are avoided. After good digestion has been established and the food intake is adequate, growth in muscle and bone will follow readily enough.

It has been found wise, particularly when dealing with the very small child, to give oxygen and carbon dioxide (6 per cent) for a few minutes before and after each feeding. This seems to prevent attacks of cyanosis when food is introduced into the stomach, and if cyanosis does occur, that feeding is stopped.

Dehydration.—Another troublesome feature of premature infant care is the tendency toward dehydration which is often neither fully appreciated nor recognized early enough by the pediatrician. Careful palpation of the fontanels and sutures is more certain to give earlier information of the development of this condition than skin turgor and elasticity. When it occurs, our first procedure is to increase fluids by mouth by means of gavage feeding if this is not already employed. Subcutaneous injection of fluids, such as saline or plasma, is not attempted routinely for the reason that a number of bitter experiences have convinced us that too many skin punctures are both serious and dangerous, leading to subcutaneous abscesses. The subcutaneous tissue in premature babies does not tolerate distention well.

Infection.—All infections must be guarded against. When it is realized that incipient infection may be present without local tissue reaction, fever, or changes in white blood cells, we should be doubly alert in our handling of premature babies. The skin of these small infants is particularly vulnerable. Overheating, rough clothes, brusque handling, and meddlesome surgical procedures have a tendency to irritate the skin and so should be avoided. Impetigo and miliaria, forms of staphylococcic infection, are not only troublesome but also dangerous.[8]

We have been continually amazed during the past fifteen years by the apparent unsusceptibility of previable babies to upper respiratory infections even during periods of high incidence in the general population and in the presence of milder attacks in the mother.[9, 10] When pneumonia developed, most of the cases were of the lipoid variety and were usually either the result of insufflation of food, amniotic debris, vaginal secretion, or a terminal phase of sepsis. In the latter condition, the *Staphylococcus aureus* is the most frequent offender followed in importance by colon bacillus, hemolytic streptococcus and *Streptococcus viridans.* The portal of entry is not always found, but the organisms can gain entrance to the blood stream through abrasions of the skin, through the cord stump, through the gastrointestinal, pulmonary and genitourinary tracts, and because of careless intravenous and subcutaneous injections. The development of diarrhea in these babies is extremely hazardous to their survival, and overfeeding in the first few days of life is often a contributing factor. However, *S. hemolyticus, Bacillus pyocyaneus,* and *B. coli* have been cultured from both the stools and blood when this condition occurs. Usually a breakdown of the nursery aseptic technique has been at fault, but fortunately this occurrence has been extremely rare. Clean hands and hair on the part of all those handling the babies, exclusion from the nursery of all persons suffering from respiratory or skin infections, no matter how mild, careful supervision of the formulas and their sterility, and individual utensils for each baby comprise the backbone of our nursery technique. For a number of years, caps and masks have been eliminated because of their questionable value in preventing the spread of infection, and the results have appeared to justify this action.

Environment.—The provision for and maintenance of an environment comparable to the protective maternal one from which he has so abruptly been separated is of vital importance to the baby. It is not only necessary to prevent

subnormal temperatures but also to avoid the development of fever in the premature infant, for either can be equally dangerous. The temperature of the incubator or hot bed should be so regulated as to provide the utmost comfort and at the same time to maintain the baby's temperature between 98 and 100° F. which, from our observation, appears to be ideal. The latter should be checked rectally every three hours until such time as stabilization becomes evident. Premature jackets help in conserving the body heat, but are not mandatory, and do prevent motion. Moisture control of the environment should also be watched for it has been our experience to witness a number of small premature infants who showed great signs of discomfort when the relative humidity exceeded 50 per cent. In checking our nurseries, we have found it possible to maintain a relative humidity of between 30 and 45 per cent without any particular effort, and this moisture content has proved both adequate and satisfactory for these small babies. From time to time, they are allowed an opportunity to regulate their own body temperatures by the simple expedient of the heat being turned off temporarily or of the child being removed to an ordinary crib. It is surprising to see how quickly they can adapt themselves to the changed circumstances.

Prognosis.—When considering the ultimate prognosis of those premature babies who survive the early months, time alone will reveal the answer. In the majority of cases, it must be guarded and is dependent more on the inherent vitality of the child plus the normal development and functioning of his anatomic and physiologic processes, than upon the start in life we are able to offer in the hospital. There can be abnormal physical conditions existing at birth which are not demonstrable clinically in the first few weeks but which are detected after several months have elapsed as, for example, focal brain injury indicated by partial spasticity of an arm or leg, serious eye defects, and mental retardation with or without convulsions. The physical growth of premature babies is uncertain in the first few years. We have observed a 2-pound child at birth, who weighed only 12 pounds at one year, and 16 pounds at 2 years of age. On the other hand, several progressed normally as illustrated by a 2-pound, 2-ounce boy who weighed 20 pounds at one year, and 27 at 2 years of age. A checkup on a relatively small group of these premature infants in the Well-Baby Clinic during their first year showed them lagging behind the average full-term babies by 2 to 3 pounds.

However, no matter how dubious the outcome may be, it is still our obligation to provide the best knowledge, medical supervision, and nursing care for premature infants. Success or failure depends, in large measure, upon the efficiency and faithfulness of the nursing staff. Our hospital has been most fortunate in having the services of many nurses in charge of the nurseries who understood the problem facing them and who gave unstintedly of their time and energy in order to carry out our program. Special duty nurses on private cases have been far beyond the average in intelligence and have given competent and full care to their infant patients. It can also be stated that the obstetric and pediatric staffs have been awakened to the exceptional requirements and

ramifications of the problem and have cooperated splendidly with each other during the past fifteen years.

CONCLUSION

In this fifteen-year report on the problem of prematurity as encountered at the Philadelphia Lying-In Hospital, we have endeavored to approach the subject from the standpoints of incidence, mortality, and survival. From our statistics, only a slight annual fluctuation in the occurrence of premature babies was evident and it could not be proved that the age of the mother, race, and economic status were determining factors, whereas there was some reason to believe that competent prenatal care together with the faithful cooperation of the pregnant woman produced a favorable response. In considering the mortality rate, it became apparent that the birth weight of the baby, length of term, systemic diseases in the mother, especially toxemia, and complications of delivery including cord and placental complications, were extremely important. The methods employed in delivering these babies, with the exception of a breech presentation, assumed a less impressive position. The survival of premature infants seems to be primarily dependent upon their birth weight, the absence of severe complications before and during delivery, and skillful care during the first few weeks of life. The cautious administration of food, the avoidance of dehydration and infection, and the maintenance of a favorable environment are discussed. The ultimate prognosis of all premature infants can be determined only by time because of the possibility of the appearance later on of abnormalities that could not be ascertained during the early days of life.

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THE CRYING OF NEWLY BORN BABIES

IV. A Follow-Up Study After Additional Nursing Care Had Been Provided

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DURING April, 1944, the crying of babies in the neonatal period was observed in the nursery at one of the hospitals in Rochester, Minn. The results of this preliminary study have been published in two previous articles, one[1] devoted to the community phase and the other[2] stressing the crying of individual babies. The preliminary study was undertaken in order to learn something about the total number of minutes of crying by newly born babies in a hospital ward, the number of spells, and some of the reasons for crying, in the hope that we could find some way of decreasing this unpleasant response. As a result, we concluded that more crying was done than should be necessary to indicate distress or need. We were able also to show in another study[3] that in the hospital the number of spells of crying was far more than occurred at the babies' homes soon after dismissal from the hospital.

Since the study made in April, 1944, several pertinent changes have been made in the nursery routines and techniques with a view to ameliorating conditions for the babies. These have had the wholehearted cooperation of the nursing staff and of the hospital administration. Instead of being without wrappers as formerly, the infants are wrapped loosely in cotton blankets. Although this was intended to give the babies a feeling of security, it has almost eliminated the appearance of abrasions on the feet which resulted from rubbing against bedclothing. The mothers' supper trays now arrive shortly after 5 P.M. This change in routine permits the babies to go out for their 6 P.M. feeding on time, rather than at 7 P.M. as previously happened. The cleaning of the head nurse's room, the nursery, workroom, and floors is now done by a maid during the day instead of by nurses on duty at night. One student nurse has been added to each shift. These extra nurses have acted as trouble shooters in attending to the comfort of the babies. All nurses have become sensitized to the baby's cry so that they attempt to find out what the baby wants and try to satisfy him as soon as possible.

Another observation of newly born babies was conducted for eight days in June, 1945, in this same nursery. Again, all full-term infants were watched constantly by four observers, who took turns during each twenty-four-hour period. Since the observers were physicians or nurses, they were competent to investigate the causes of crying and to direct efforts to alleviate each situation.

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If it were felt that the infant was hungry, he was sent to his mother for feeding, was fed water in the nursery, or was given an empty bottle to suck, whenever these efforts did not conflict with the floor routine. Within practical limits the nursery routine was made flexible enough to meet the demands of each situation.

Work charts were made for each twelve hours during the entire time of observation. The crying behavior of each baby was plotted in a horizontal bar divided into twelve parts, each division representing sixty minutes. Each crying period was represented by a straight black line, above which was written the number of minutes of crying and beneath which a letter indicated the probable reason or reasons for each spell; namely, (a) hunger, (b) vomitus, (c) soiled diaper, (d) wet diaper, and (j) unknown reasons, as in the study of last year. Each period of nursing care was similarly plotted using a straight red line, above which was placed the number of minutes of care. "Nursing care" was again used as a rather general term including the time spent changing diapers, taking temperatures, or offering water, as well as the feeding time spent in the mother's or nurse's arms. However, records were kept of the actual amount of time each baby spent in his mother's room, so that the time spent in baby-tending by the nurses could be computed. These work charts gave the data which were analyzed for this report.

RESULTS

The average number of babies occupying the nursery each day was eighteen, which is two less than we had last year. The average number of minutes of crying for each baby in twenty-four hours was 55 minutes, a decrease of 51.4 per cent in the figure of 113.2 minutes determined in the study of 1944. Each baby had an average of eighteen crying spells each day; 5.7 (31.4 per cent) of these spells lasted for more than 3 minutes. This was somewhat higher than the average of four prolonged crying spells observed last year in the study of the newly born babies in the home.[3]

TABLE I. NUMBER OF CRYING SPELLS PER DAY FOR EACH CAUSE DURING THE STUDIES IN 1944 AND 1945

YEAR	NUMBER OF BABIES PER DAY	CAUSES OF CRYING						
		TOTAL SPELLS PER DAY					PROLONGED SPELLS PER DAY*	
		HUNGER	VOMITUS	SOILED DIAPER	WET DIAPER	UNKNOWN REASONS	HUNGER	UNKNOWN REASONS
1944	50	345	6	92	204	412		
		(32.6%)	(0.6%)	(8.7%)	(19.2%)	(38.9%)	(55.3%)	(19.8%)
	1	6.9	0.1	1.8	4.1	8.2	2.2	0.8
1945	18	137	5	25	88	115	61	26
		(37.0%)	(1.4%)	(6.8%)	(23.8%)	(31.1%)	(44.2%)	(22.2%)
	1	7.6	0.3	1.4	4.9	6.3	3.4	1.4

*Study in 1944 on prolonged spells of crying was made in the homes shortly after the babies left the hospital. In 1945, this study was made while the baby was still in the hospital. Crying for more than three minutes was considered prolonged crying.

While the determination of the cause or causes of each crying spell still depended on the personal judgment of each observer, since the observers were more experienced, the information was undoubtedly more nearly accurate than

that obtained in the more casual study of 1944. This may account for the increased number of instances in which there were multiple reasons for crying. Whereas each baby had only eighteen spells of crying per day, twenty reasons for crying were listed daily for the average baby. The number of crying spells in the nursery per day for each cause is shown in Table I. In the investigations of both years, hunger and unknown reasons led the list of causes of crying; but this year the incidence of crying spells due to hunger exceeded those due to unknown causes. Unknown causes were listed in 22.2 per cent of the prolonged episodes of crying. This number should be compared with 19.8 per cent in the study made of the children in their homes in 1944.[3] Hunger, on the other hand, accounted for 44.2 per cent of the prolonged spells of crying in the nursery, whereas in the home the mothers estimated this figure at 55.3 per cent. In studying the number of minutes of crying for the total group per day ascribed to each cause (Table II) we found that hunger caused 53.2 per cent of such time and that unknown reasons, the next highest factor, dropped down to 23.3 per cent.

TABLE II. MINUTES OF CRYING PER DAY FOR EACH CAUSE DURING THE STUDIES IN 1944 AND 1945

YEAR	NUMBER OF BABIES PER DAY	CAUSES OF CRYING				
		HUNGER	VOMITUS	SOILED DIAPER	WET DIAPER	UNKNOWN REASONS
1944	50	2,024.2 (35.5%)	26.7 (0.5%)	474.8 (8.3%)	1,169.9 (20.6%)	2,000.6 (35.1%)
	1	40.5	0.5	9.5	23.4	40.0
1945	18	533.7 (53.2%)	5.2 (0.5%)	64.2 (6.4%)	166.2 (16.6%)	233.3 (23.3%)
	1	29.6	0.3	3.6	9.2	13.0

Whereas all of the values for the study in 1945 were less than those for 1944, we found considerable change in the percentage of crying for which each cause was responsible. Thus, while in 1944, hunger accounted for 35.5 per cent of the minutes of crying each day, this figure rose to 53.2 per cent in 1945. While the amount of time due to unknown reasons was 35.1 per cent in 1944, it dropped to 23.3 per cent in 1945. This may be interpreted to mean that the ameliorating regimen stopped much of the crying due to unknown, perhaps less compelling causes, whereas it was unable to quiet babies under the influence of a basic demand like hunger.

During the process of analyzing the data, the sum of all the minutes of crying of all the babies for each hour of the day was determined. From this material the average amount of crying for each baby per hour was calculated. We have summarized these data in Fig. 1 and have included the hourly distribution of crying during the study in 1944. The general reduction in crying demonstrated during this study is shown clearly in Fig. 1. But in two periods of the day in 1945, from eight to ten o'clock in the morning and in the evening, two new peaks of crying appear in the graph. Both of these may be explained by the nursing routines. After the nurses receive the morning report at 7:30 A.M., they come into the nursery to give the babies their morning care. The nurses take the babies' temperatures, clean them, weigh them, and put clean

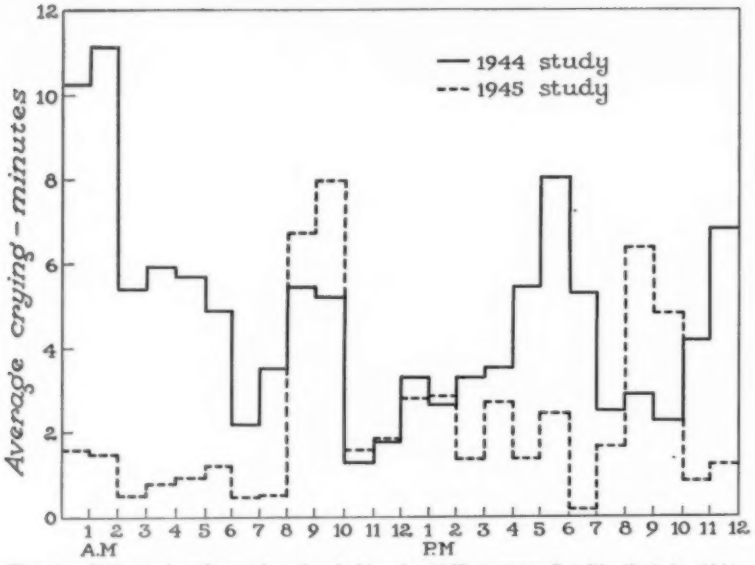

Fig. 1.—Average hourly crying for babies in 1945 compared with that in 1944.

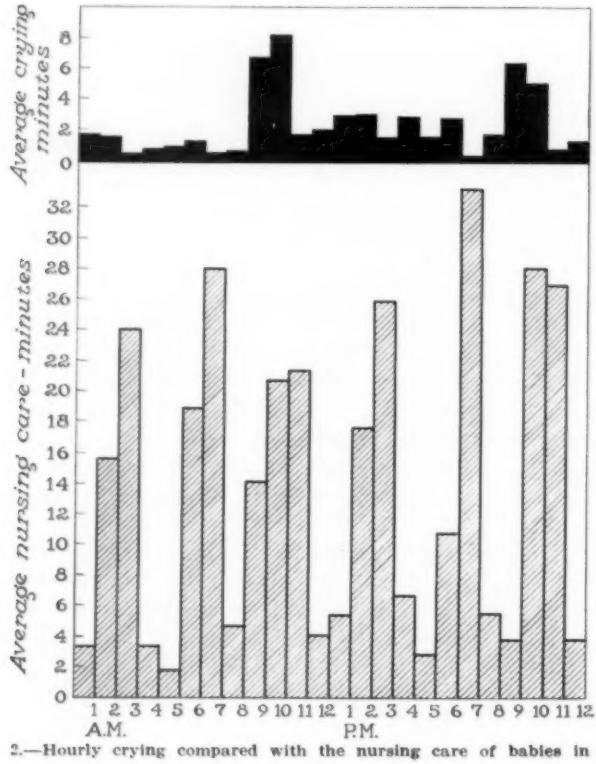

Fig. 2.—Hourly crying compared with the nursing care of babies in 1945.

clothing on them. During this process each baby is thoroughly awakened, after which he is put back into his crib to wait until 10 A.M. for feeding. It is obvious that crying might increase at that time. In the evening any babies who become hungry or uncomfortable must await departure of visitors and routine care of the mothers before they can be taken into their mothers' rooms for comfort or feeding. We feel that these two periods of crying, which exceed the corresponding periods in 1944, can be corrected by appropriate changes in the nursery routines and that with this modification we can still further reduce the amount of crying in the newborn nursery.

The hourly amount of nursing care given each baby was calculated, and these figures were plotted against the amount of crying in the same hours. This is shown in Fig. 2. The spacing of the pillars of nursing care which indicate feeding times is now nearly equal, an improvement over the graph made from the study in 1944 where it was unequal. However, the reciprocal relationship between crying and nursing care is still evident.

By comparing Fig. 2 with the graph made from the study in 1944 the increase in the total amount of nursing care is evident immediately. By actual calculation we found that each baby in the nursery this year received five and one-half hours of care each day. This is seventy-three minutes more than the daily nursing care given each baby in 1944.

However, so far in our calculations nursing care has included the amount of time spent by the babies in their mothers' rooms, so that this five and one-half hours of nursing care were not entirely given by the student and graduate nurses; much of it was provided by mothers. In order to calculate the actual amount of professional care given to babies it was necessary to find out the time spent by each baby in his mother's room. Study of this factor revealed that the mother alone cared for the baby for 3.6 hours daily. Subtracting this 3.6 hours from 5.5 hours, we find that 1.9 hour each day was devoted to each baby by the nurses. Similar calculations reveal that in the 1944 study 0.7 hour each day was devoted to each baby by the nurses. When only 0.7 hour of nursing care was given daily to each baby, the average infant cried 113.2 minutes per day. With an increase to 1.9 hours of care the crying time dropped to 55 minutes.

It may be of interest to know that during the 1945 study 79.3 nurse hours were available each day. These hours are exclusive of those of the supervisor and those of the personnel in the milk laboratory. It is easy to calculate from this that the actual amount of time spent by the nurses with the babies each day was 43.1 per cent of the available time.

The question may be asked how many times does the nurse pick up the baby each day. Our data show fifteen times. In 89.8 per cent of the times that the baby was picked up, the care given took longer than three minutes. Hence, we know that when the nurse picks up a baby for any purpose, it can be expected to take her longer than three minutes.

COMMENT

In our consideration of the neonatal crying problems we have assumed the cry of the newly born baby as an individualized form of self-expression, used

as a signal of need to whomever takes care of him. The cry occurs in response to extrinsic or intrinsic stimuli.

By making changes in the nursing and floor routines, adding more nurses, and individualizing the care, crying in the neonatal period was reduced 51.4 per cent and we estimate that as a result of this study more changes in the nursing routines may come which can further improve the babies' comfort during the stay in the hospital.

It was found in a previous study[1] that barometric pressure might possibly have some effect on the amount of crying, but since the barometric pressure was consistently higher during the study in 1945 than in 1944, and since we had a decrease in the amount of crying in the 1945 study, this factor cannot have been of any great significance.

Hunger and unknown reasons remain the most important causes for crying. It is apparent from the increased percentage of the crying for hunger that this factor must be treated appropriately by feeding the baby when he shows the need for food. Such treatment will require modifications of nursery routines in most institutions. However, it will still be possible, by paying more attention to the cry, to reduce the amount due to unknown reasons. This will mean more individualization in the care of each baby.

The actual amount of daily nursing care was 1.9 hours for each baby this year in contrast to the meager 0.7 hours last year. Considering the helpless condition of a newly born baby, we feel that increasing the amount of effective nursing care available to these infants is justified. We seem to be approaching the optimum, but still further changes will decrease the crying.

SUMMARY

A study of the crying in the nursery for newly born babies at one of the hospitals in Rochester, Minnesota, was done after making more nursing care available and individualizing the babies' care. The study was based on data obtained from continuous observation for eight days.

The average amount of crying for each baby was 55 minutes each day in contrast to 113.2 minutes during the study in 1944. The average number of times each baby cried daily was eighteen, of which 5.7 were prolonged spells, that is, crying lasted more than 3 minutes.

Hunger led the list of causes for crying, but unknown reasons was close behind. Wet diaper, soiled diaper, and vomiting remain in that order as minor causes of crying.

The actual amount of nursing care given each baby daily was 1.9 hours in contrast to 0.7 hours during the study in 1944. This was 43.1 per cent of the available nursing time.

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INTRACISTERNAL PENICILLIN

Observations of Its Effect on Dogs

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THE reading of the article, "Intraventricular Penicillin: A Note of Warning,"[1] having aroused interest in the possible deleterious effect of penicillin on the central nervous system, it was decided to observe the effect on dogs of intracisternal injections of the drug, and the following experiment was begun. Shortly afterward, Walker and Johnson[2] published further work along the same lines, and this report constitutes a corroboration of their findings and the recording of certain additional observations not included in their article.

Dogs were lightly anesthetized with intravenous pentothal sodium, and observing the usual aseptic precautions, intracisternal taps were executed. These were done at twenty-four to forty-eight hour intervals, and on each occasion, instillation of the test solution was preceded by withdrawal of a corresponding volume of cerebrospinal fluid. Reactions following each instillation were noted, and the cisternal fluid was examined.

The control experiments were performed on six dogs, average weight 23.5 pounds. Injections were of 5 c.c. sterile normal saline solution, each animal receiving from five to seven injections. From a total of thirty-eight injections, five instances of brief stiffening of the extremities and sometimes of the neck also, lasting for only a few minutes, were noted in three dogs. No convulsions occurred, nor were other reactions observed. The cerebrospinal fluid showed only irregular slight increases in leucocyte content, with the predominant cell being of the mononuclear variety. Higher rises on a few occasions may have been due to infection and were concurrent with the only positive Pandy reactions and sugar content alterations seen in the series. Two of the dogs were sacrificed and autopsies were done. Histologic changes were not observed in the brains, cervical cords, or meninges.

The second group of animals consisted of six dogs, average weight 20.3 pounds. Instillations were of 5,000 units of penicillin in 1 c.c. sterile normal saline solution. One dog received five such injections; another, eight; a third, nine; and the remaining three, ten each. From a total of fifty-two injections, there occurred a total of ten (19.2 per cent) convulsive reactions of which six were mild (e.g., facial twitchings, snapping of jaws, frothing, defecation), and the remaining four, minimal (e.g., facial twitchings with or without frothing). No convulsions occurred with the first dose of the drug. Two of the six dogs failed to convulse. The number of leucocytes in the cerebrospinal fluid was

From the Department of Pediatrics, Duke University School of Medicine. Thanks are due to Drs. George O. Boucher, and Keith M. Oliver for assistance in performing these experiments; to Dr. Walter G. Gobbel, Jr., who made the histopathologic observations; to Dr. Wiley D. Forbus, who critically reviewed the microscopic sections; and to Dr. Jay M. Arena for encouragement and helpful suggestions during the course of the work.

again not elevated above that of the control series. No abnormalities were discovered with the Pandy or Benedict reactions. Pathologic sections were not remarkable in two of the dogs, of which one had had convulsions, and one had not. Another dog showed a minimal meningitis, plus a rather profuse hemorrhage into one of the lateral columns of the cervical cord, in which the red blood cells were accompanied by numerous, small round cells and macrophages, and a few polymorphonuclear leucocytes. A fourth dog showed, in several areas over the cerebral cortex, minimal subarachnoid accumulations of small round cells and polymorphonuclear leucocytes, together with several small areas of hemorrhage into the cervical cord. The fifth dog showed a minimal inflammatory process involving the pia-arachnoid, together with a hemorrhage into the brain substance extending caudad from the rostral part of the medulla. The sixth dog supplied the only instance of an acute purulent meningitis, the process involving the pia-arachnoid, chiefly over the inferior portion of both temporal lobes, but extending also over the frontal, parietal, and cerebellar lobes, bilaterally. The exudate consisted in large numbers of polymorphonuclear leucocytes, among which were many eosinophiles and some mononuclear cells. No bacteria were demonstrated in the sections.

The third group of dogs consisted of four animals selected, after a rest period of five days, from the control group. Average weight was 23.5 pounds, and individual states of health appeared excellent. One dog received eight injections; the other three dogs received nine injections each of 10,000 units of penicillin in 2 c.c. sterile normal saline solution. From a total of thirty-five injections, severe convulsions (although not so violent as those noted in the fourth group) were observed in seven instances, a moderately severe convulsion in one instance, and mild convulsions in sixteen instances, for a total incidence of twenty-four reactions, or 68.6 per cent. Again no convulsions occurred with the first dose of the drug. No dog in the group failed to convulse. The cerebrospinal fluid did not differ, significantly, in leucocyte content from that of the control series, nor were globulin and sugar contents appreciably altered. Post-mortem studies revealed no lesions in three of the dogs, but in the fourth, a small area was found in the cerebral cortex in which there was moderate perivascular cuffing by round cells, together with a few scattered cells of similar type in the subarachnoid space.

The fourth group consisted of only two dogs, one of which received two injections of 100,000 units of penicillin in 5 c.c. sterile normal saline solution. The other dog received similar doses four times in the lumbar region, the fifth dose being administered by the cisternal route. Since no cerebrospinal fluid could be obtained at the time of any of the lumbar injections, it is doubtful that the drug reached the subarachnoid space in these instances. Although anesthetized, both dogs whimpered as if in pain during intracisternal instillation of the penicillin. Severe convulsions, beginning two minutes after injection, occurred after the second injection in the first dog; in the second dog, no reaction followed four lumbar (intramuscular ?) injections of the drug, but convulsions, equally severe, began seven minutes after the first intracisternal injection. Convulsions in both dogs began as facial twitchings, followed in rapid progression

by generalized seizures, consisting of violent clonic movements of the extremities and neck, with forceful striking of the head against the concrete floor, snapping of the jaws, excessive salivation, defecation, labored respirations, cyanosis, and apparent blindness. Death followed the convulsions of the first dog, while the other remained moribund for seventy-two hours and was sacrificed. Cerebrospinal fluid studies were too inadequate to permit conclusions to be drawn. Postmortem examination of the first dog revealed only moderate congestion of the meningeal vessels. Numerous small infarcts were found, however, throughout the brain and cervical cord of the second dog, especially in the medulla and cervical cord, and in these areas were noted a few small round cells, some of them forming a perivascular cuff. There were, in addition, several subarachnoid accumulations, all minimal, of small round cells, plasma cells, and occasional polymorphonuclear leucocytes.

It was noted that all convulsions, regardless of degree of severity, were preceded by a sort of aura in which the dog appeared preoccupied, stared vacantly, lowered his head, and if disturbed, snapped irritably at the aggressor. During those convulsions sufficiently mild to permit maintenance of equilibrium, vision seemed seriously impaired, so that the dogs collided repeatedly with obstacles in their paths. Sight was restored at the end of the convulsion. A period of extreme apprehension and excitability followed most of the convulsions.

CONCLUSIONS

1. Convulsive reactions to intracisternally administered commercial penicillin were observed in dogs, corroborating reports in the recent literature.

2. Histopathologic studies revealed several instances of hemorrhage into the brain substance, with multiple cortical infarcts in one animal. Also noted, was the occurrence in several dogs of minimal meningitis and perivascular round cell cuffing, as well as one instance of acute purulent meningitis.

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GALACTEMIA

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IN 1917, Goppert[1] described a chronically ill child, with a background of liver disease, who was found unable to tolerate galatose and who thrived only when lactose was removed from his diet. In 1935, Mason and Turner[2] presented a similar case with extensive carbohydrate studies, and more recently Norman and Fashena[3] presented a third. Two more cases hitherto unpublished are in the records of the Harriet Lane Home.[4] A sixth case has recently been published by Mellinkoff and associates[5] and a seventh case has been reported recently by Bruck and Rapoport.[6] We shall describe two additional cases in which this condition occurred. The metabolic anomaly found in these children is undoubtedly rare, but it probably occurs oftener than the paucity of records would suggest. A composite picture of this symptom complex includes (1) athrepsia with insatiable hunger, (2) hepatomegaly, (3) lamellar cataracts, (4) galactosuria, and (5) mental retardation. All but the last are probably constant findings. This condition should be considered as a possible diagnosis whenever hepatomegaly, inanition, cataract, and melituria are encountered in young infants. The diagnosis is readily made if the reducing substances in the urine are properly identified. We present two patients in whom these features were found. These cases will be discussed with regard to present concepts of galactose metabolism and of galactose cataractogenesis which are now briefly reviewed.

Endogenous galactose occurs in certain constituents of nerve tissue, the galactolipids or cerebrosides. It is not known how they function and how necessary they are, but some writers consider them essential, and they argue teleologically that galactose exists in milk so that the nursling may use its available galactose in the formation of nerve tissue, especially in the myelinization which occurs at a rapid rate in the first six weeks of life.[7] It is possible that the body can synthesize galactose for this purpose. Certainly galactose is synthesized in the lactating breast.[8]

Exogenous galactose is ingested chiefly or entirely as one fraction of the lactose molecule in milk. Absorption of galactose takes place in the small intestine. This process is thought to consist of a phosphorylation of the sugar in the intestinal mucosa, which increases the gradient of diffusion of the sugar into the mucosal cells. This is an active physiologic process as it is with glucose and not the mere physical diffusion by which all other monosaccharides enter the portal circulation. The absorption of galactose is somewhat more rapid than the absorption of glucose. The process is limited quantitatively and the simultaneous absorption of one sugar inhibits to some extent the absorption of the other.[9]

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Read at the Seventy-Sixth Annual Meeting of the Canadian Medical Association, Montreal, June 14, 1945.

The galactose proceeds to the liver where it undergoes conversion to glucose and to glycogen. The intermediate steps by which this occurs are not fully known. Glucose –1– phosphate and galactose –1– phosphate are both present in the liver during galactose assimilation, although there is no progressive accumulation of the latter phosphate. There is an increase in reducing phosphoric esters, particularly glucose –6– phosphate. The increased glucose content of the liver during galactose assimilation would seem to demonstrate the conversion of galactose to glucose. All of the above-mentioned substances probably participate in this conversion.[10] It is doubtful whether glycogen formation takes place only after the galactose has become converted to glucose; for the glycogen thus formed varies in certain respects from that formed directly from glucose: the molecular size of the former corresponds to 18 glucose units, whereas that of the latter corresponds to 12 glucose units, and, once formed, the former undergoes glycogenolysis more slowly than the latter.[11] An enzyme system in the liver for the conversion of galactose into glucose and glycogen has been inferred but not demonstrated. The normal liver can convert galactose at a certain rate; the galactose tolerance test has thus become used as a measure of liver function.

The galactose not assimilated by the liver remains in the blood and can be demonstrated in the systemic circulation. Its fate thereafter, apart from excretion by the kidneys, is disputed. It has been shown that a frog spinal cord can metabolize galactose faster than glucose when it is at rest and slower than glucose when it is being stimulated.[8] Galactose can be utilized by diabetics and has an antiketogenic effect.[12, 13] There is a difference between the arterial and venous levels of galactose during galactose assimilation.[8] Finally the hepatectomized dog is able to metabolize certain amounts of galactose.[14] These facts suggest the possibility of extrahepatic utilization of galactose; however, this probably does not occur on any large scale. Galactose produces a steeper and higher rise in the respiratory quotient than does glucose.[14] This suggests that, either at the hepatic level or in the tissues, galactose is utilized apart from being converted into glucose. The galactose remaining in the arterial blood is excreted by the kidneys even at a low blood concentration so that there is no appreciable renal threshold for galactose. It has been found that the renal tubules of the dog absorb about 40 per cent of the galactose that appears in the glomerular filtrate.[15]

The interest in the relation between galactose and cataract formation began in 1935, with the accidental finding in an unrelated experiment that cataract developed in all rats that received a 70 per cent lactose ration.[16] Three years earlier Kirby and associates[17] had made the important observation that galactose had a direct toxic effect on lens epithelium cultivated in vitro. Feeding a high galactose ration became the standard method of producing cataract in experimental animals.

The changes in the lens occurring as a result of galactose administration are as follows: The earliest microscopic changes involve first the cortical fibers near the equator, then the capsular epithelium and finally the nucleus. Macroscopically there is first ciliary hyperemia, then the appearance of fluid droplets in the peripheral lens tissue, and eventually opacity sets in under the capsule

and in the central nuclear portion.[18, 19] Some workers[20, 21] found senile suture lines. The permeability of the lens capsule has been variously found increased[21] and decreased.[22] The precise changes vary with the species and age of the animal utilized. For example, young albino rats develop nuclear cataract and older rats develop cortical cataract.[23] On withdrawing galactose the cortical opacity may clear, but nuclear opacity remains.[24]

The chemical changes in the lens following galactose administration have also been studied. There is an increase in total ash with more sodium, calcium, sulfate, and carbonate, but less potassium, phosphate, and chlorine. The water content increases. The anions increase more than the cations.[25] The organic changes, however, seem to reflect more closely the essential disturbance. Galactose causes a loss of glutathione, cystin, and vitamin C from the lens; the reduction in the sulfhydryl and vitamin C content precedes any sign of cataract.[26] The electrical potential in young rat lenses rises in the central portion, a phenomenon which accompanies loss of oxidation-reduction systems and a decrease of metabolic activity.[27] It may be noted that many of these changes, such as the rapid development of senile suture lines, the type of mineral content change, the loss of sulfhydryls, and the rise in electrical potentials, are manifestations of tissue senescence and death and are similar to what occurs in senile cataract. It has not been demonstrated that any of these changes are specific for galactose-produced cataract. In other words, galactose poisons the lens, thus confirming the original in vitro observation by Kirby and associates.[17] There is no reason to believe that any of these changes explain the action of galactose. Thus it might be preferable to think that the sulfhydryl content of the lens has dropped because the lens has been damaged rather than that the lens has been rendered cataractous because of the sulfhydryl loss.

The reputed influence of galactose upon calcium metabolism, plus the well-known incidence of cataract in certain disorders of calcium metabolism, have suggested to some workers[23] that the explanation of galactose cataract may lie near-by. There has been no general agreement upon the numerous theories developed in this field.

*CASE 1.—G. D. This child was first seen when he was 6 months old. He was the second child of young parents in good health; the first child was considered normal. The delivery was at term and not unusual. The baby weighed 7½ pounds at birth; he soon became jaundiced and remained so for two or three weeks. The baby was always considered a feeding problem; he often refused feedings, cried a great deal after meals and before bowel movements, and frequently had a distended abdomen. He did not vomit, however, and only occasionally had loose watery stools. Frequent formula changes reflected these difficulties: he had been nursed for the first three weeks and was then given various formulas of evaporated milk, cow's milk, and condensed milk. Because of his failure to thrive, he was brought to Montreal and admitted to the Children's Memorial Hospital on April 25, 1939.

Physical examination revealed an irritable, emaciated, male infant who weighed 8½ pounds, only one pound above birth weight, and who seemed to be younger than his age of 6 months. There was a marked lack of muscle tone. The eyes showed bilateral cataracts with dense central opacities. Nothing unusual was found on examination of the upper respiratory tract or the thorax. The liver was enlarged, the edge reaching below the umbilical level. The tip of the spleen was just palpable.

*Patient on the service of Dr. Alan Ross, presented here with his kind permission.

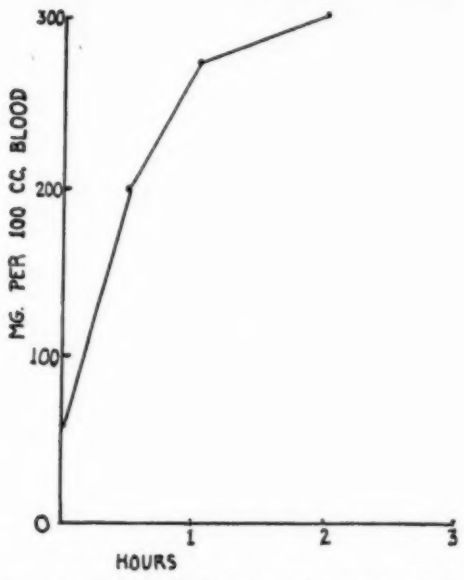

Fig. 1.—Total blood sugar values following ingestion of 1.75 Gm. of glucose per kilogram of body weight. (G. D. May 2, 1939.)

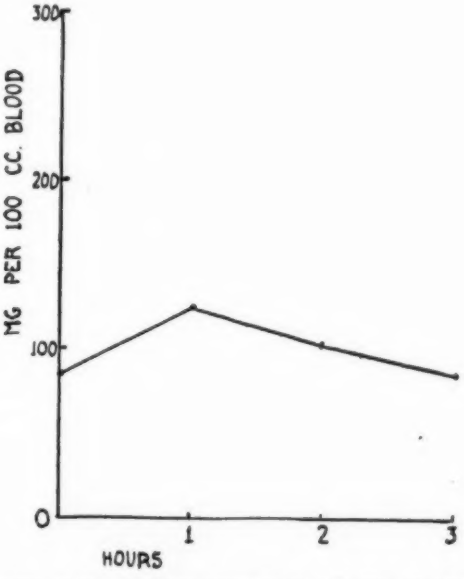

Fig. 2.—Total blood sugar values following ingestion of 1.75 Gm. of glucose per kilogram of body weight. (G. D. March 15, 1940.)

The laboratory findings were the following: The blood Wassermann and Mantoux tests were negative. The red cell count was 4.5 million, the hemoglobin, 14.3 Gm. per 100 c.c., and the white cell count, 23,900. Specimens of urine showed albumin in amounts varying from 75 to 400 mg. per cent and occasional leucocytes and hyaline casts on microscopic examination. No bile, urobilin, or acetone was found. The most arresting laboratory finding was the urinary sugar, which ranged from 1 to 3 per cent. The fasting blood sugar was 59 mg. per cent.

The indirect Van den Bergh was 3.0 units; the direct, 0 units. The blood calcium was 10.2 mg. per cent, the phosphorus, 4.8 mg. per cent. There were 30 mg. per cent of nonprotein nitrogen in the blood plasma. There were 5.6 Gm. per 100 c.c. of total protein in the plasma, of which 4.62 Gm. per 100 c.c. were albumin, 0.52 Gm. per 100 c.c. globulin, and 0.46 Gm. per 100 c.c. fibrinogen. The blood cholesterol was 125 mg. per cent. Roentgenographic examinations of the chest and skull revealed nothing remarkable. The bones were generally decalcified.

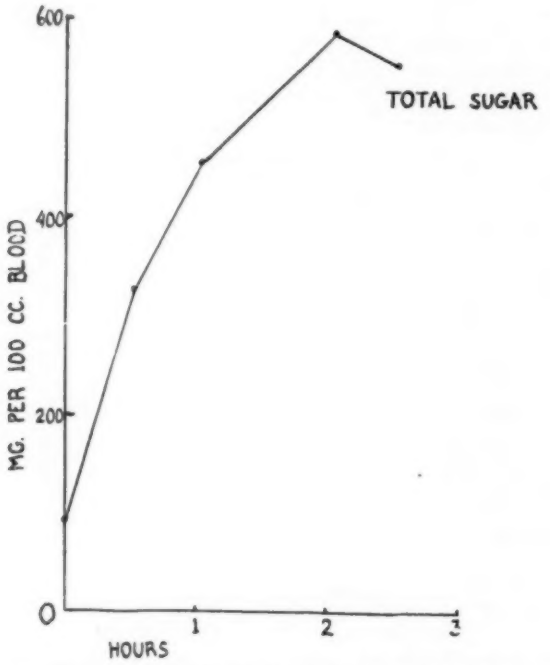

Fig. 3.—Total blood sugar values following ingestion of 1.75 Gm. of galactose per kilogram of body weight. (G. D. May 23, 1939.)

The melituria raised the question of diabetes. But when repeated examination of the baby's glucose tolerance (Figs. 1 and 2) failed to confirm this diagnosis, it was suggested that this case might be similar to the case reported by Mason and Turner.[2] Identification of the sugar in the urine was therefore undertaken. When subjected to the action of baker's yeast, the sugar did not ferment. The reducing power of this sugar was not increased by acid hydrolysis; this ruled out the presence of disaccharides. Osazone crystals were then prepared which were identical with those of galactosazone. Mucic acid crystals identical with those prepared from galactose were obtained.

While the identity of the reducing substance in the urine was thus being established as galactose, a striking defect in the child's galactose tolerance was demonstrated by a curve in which the blood galactose reached a peak of 588 mg. per cent and was still above 500 mg. per cent two and one-half hours after the ingestion of galactose (Fig. 3). This hypergalactosemia and the galactosuria were accepted as proof of the baby's intolerance to galactose. Studies of the child's carbohydrate metabolism, carried out along the lines followed by Mason and Turner,[2] are reported in detail.

Course.—On the basis of the diagnosis of galactose intolerance, the child was given a lactose-free diet, consisting of cereal, vegetable, egg yolk, and a formula made from Sobee (a proprietary soybean flour) and corn syrup. The sugar and albumin were found to have disappeared from the urine three days later. The child then began to thrive; and in spite of several attacks of otitis media requiring sulfonamide therapy and numerous myringotomies, he gained four pounds in the next three months. He continued to do well in spite of mumps, chicken pox, and further respiratory infections, including pneumonia at least twice. He spent several months in a convalescent hospital, and two weeks in a contagious disease hospital when suspected of having pertussis. When the child returned to the Children's Memorial Hospital at 14 months of age, it was found that his liver was a little smaller, the cataracts were possibly less dense, and the Van den Bergh had become normal. The bones were still quite decalcified, although the fontanel had closed. When 18 months old, the child weighed 20 pounds, had five teeth, but was still unable to sit alone. He could apparently see moving objects and would reach for them. The cataracts were now definitely less dense than on admission. The liver was only 1 cm. below the costal margin. The child was discharged at the age of 20 months on a lactose-free diet, consisting of egg, meat, fruit, vegetables, cereals, and gelatin puddings made without milk, with a supplement of dicalcium phosphate and adequate vitamins.

When 6½ years old, the boy was readmitted to the Children's Memorial Hospital on May 31, 1945, for observation and for treatment of the cataracts which had persisted. He had adhered strictly to a milk-free diet in the interval. He had remained well until he contracted pertussis in December, 1944. In March 1945, he developed a choreiform disturbance, apparently mild, which subsided in a few weeks. His development had been slow. He sat alone soon after leaving the hospital, at about 20 months of age and began to walk at 27 months of age. He began to talk at a later date and learned slowly. He could not see very well and was not skillful with his hands. He was not considered able to begin school.

Physical examination revealed a well-nourished active boy 6½ years of age, who weighed 48 pounds. Lamellar cataracts with a few peripheral striae were present. The edge of the liver could be felt 2 cm. below the costal margin. It was difficult to assess the child's intelligence because of the impairment of vision and the presence of a speech defect, but he was considered somewhat mentally retarded.

The cataracts were needled and the lenses evacuated.

Examination of the blood chemistry yielded the following information: the bilirubin level was normal, the total protein 7.66 Gm. per 100 c.c. of which 4.00 Gm. were albumin and 3.61 Gm. were globulin. The prothrombin time was within normal limits and a cephalin flocculation test was normal. The long bones were x-rayed and found to be normal. The galactose tolerance was re-examined (Fig. 7) and found to have improved somewhat since the last examination five years earlier (Fig. 4).

Carbohydrate Studies.—In the first glucose tolerance test (Fig. 1) a curve not unlike that of diabetes mellitus was obtained, though the low fasting level was unusual. The latter, coupled with the massive hepatomegaly, suggested a glycogen storage disease; but an adequate elevation of blood sugar in response to an injection of epinephrine ruled this out, and confirmed the initial objection that the hyperglycemia in the tolerance test and the absence of ketosis were incompatible with von Gierke's disease. Subsequent glucose tolerance curves demonstrated an excessive rise in the blood sugar but a fairly adequate recovery to within normal limits. These findings were considered characteristic of a state of starvation: the

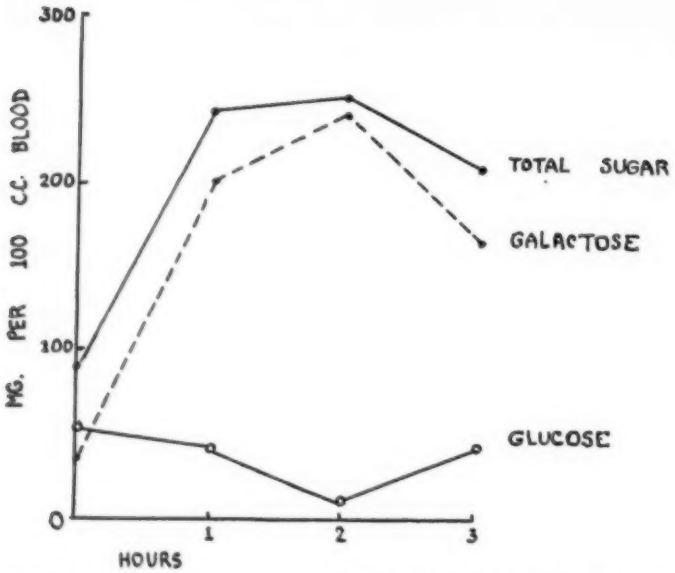

Fig. 4.—Values for total blood sugar, galactose, and glucose following ingestion of 1.75 Gm. of galactose per kilogram of body weight. (G. D. Jan. 30, 1940.)

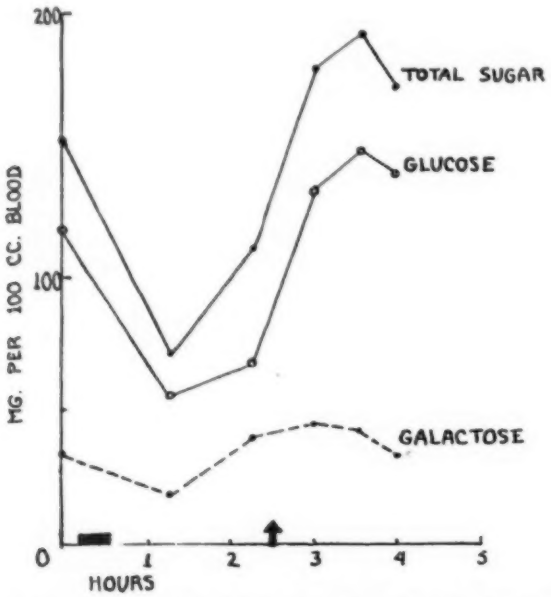

Fig. 5.—Values for total blood sugar, galactose, and glucose. Each heavy line along the abscissa represents the ingestion of a meal containing 200 c.c. of milk and 10 Gm. of lactose. The arrow indicates the subcutaneous administration of 5 minims of a 1:1,000 solution of epinephrine. (G. D. April 24, 1940.)

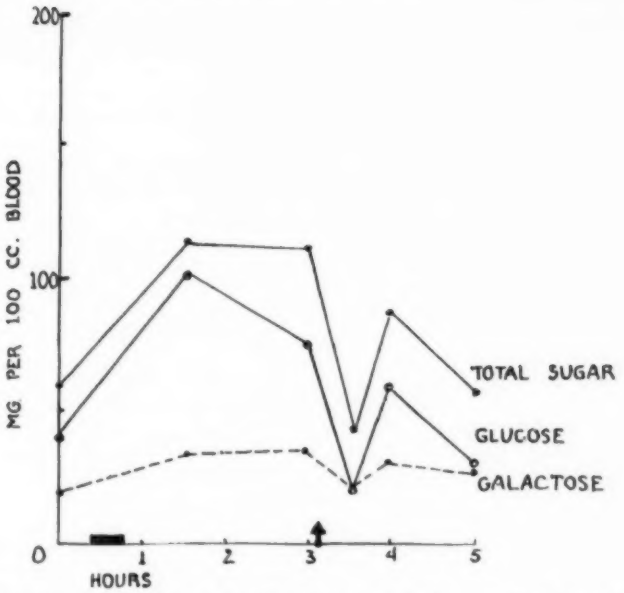

Fig. 6.—Values for total blood sugar, galactose, and glucose. The arrow indicates the subcutaneous administration of 5 units of insulin. The meal contained 200 c.c. of milk and 10 Gm. of lactose. (G. D. April 25, 1940.)

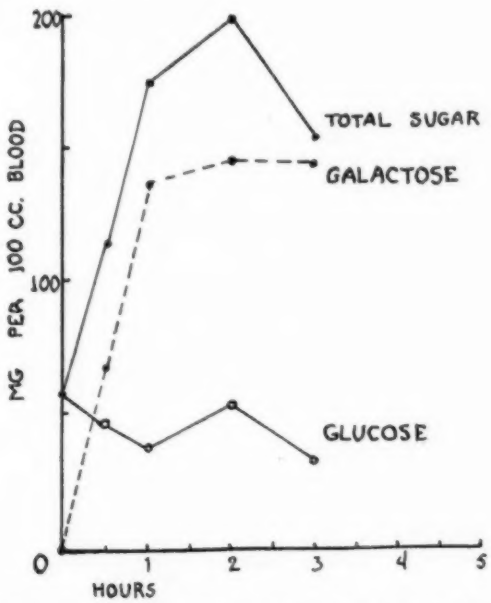

Fig. 7.—Values for total blood sugar, galactose, and glucose following ingestion of 1.75 Gm. of galactose per kilogram of body weight. (G. D. June 5, 1945.)

child's nutritional status was remaining unsatisfactory and he was still eating poorly. This conclusion was justified by a normal glucose curve obtained ten months later when good nutrition had been established (Fig. 2).

The identification of the urinary sugar as galactose and the demonstration of greatly impaired galactose tolerance (Fig. 3) showed that we were dealing with a case of galactemia. A second galactose tolerance test eight months later, the patient having been on a lactose-free diet in this interval and now in greatly improved health, appeared to show that his tolerance for galactose had increased somewhat, although it remained well below normal. The blood sugar values at this examination (Fig. 4) were fractionated by fermentation with yeast. Here a depression of the level of blood glucose accompanied the peak of the curve of the galactose fraction. This was more marked than the corresponding finding by Mason and Turner,[2] and much greater than the depression of blood glucose which galactose can apparently cause in a normal person.[7] Epinephrine raised the level of blood galactose a negligible amount, while it had the usual effect on blood glucose (Fig. 5). Insulin lowered the level of blood galactose slightly, while producing the usual depression of blood glucose (Fig. 6). We did not observe the elevation of blood galactose produced by insulin in Mason and Turner's case; however, the first blood determination was unfortunately made as late as one-half hour after the injection of insulin, so that any earlier rise would have been missed.

When the boy was readmitted five years later, the galactose tolerance was examined again (Fig. 7). It had improved; the peak value for blood galactose was found to be 146 mg. per cent as compared with 240 mg. per cent on the last examination (Fig. 4).

CASE 2.—M. D. This baby was first seen when she was 3½ months old. The first child of healthy young parents, she was delivered at home at full term. She weighed 6 pounds, appeared normal, and did not develop neonatal jaundice. One subcutaneous injection of BCG vaccine was administered soon after birth. The infant did poorly from the beginning; she vomited a considerable part of her intake and had frequent watery stools. She became ill with cough and fever twice in the first three months. Because the grandmother was blind, the mother worried about the baby's eyes and watched them closely, but she noticed nothing unusual until the baby was 3 months old; then she thought she detected cataracts. The baby was admitted to the Children's Memorial Hospital on Sept. 25, 1944, at the age of 3½ months, having gained only 12 ounces above birth weight.

Physical examination revealed a pale, marantic, and irritable infant, who was poorly nourished and developed and weighed 6 pounds, 12 ounces. The heart and lungs seemed normal. The upper respiratory tract was not remarkable though there was a small amount of nasal discharge and a somewhat dull left eardrum. The abdomen was prominent, due evidently to the great size of the liver which reached almost to the iliac crest and extended 3 cm. below the costal margin in the left midclavicular line. It had a smooth surface and a hard edge. Bilateral pinpoint cataracts were present.

The laboratory findings were the following: There was a moderate anemia, with 8 Gm. of hemoglobin per 100 c.c. of blood. The leucocyte count and differential were normal for the age. The blood Wassermann was negative; so was the Mantoux test, although the BCG vaccination had been done only three months earlier. A routine admission urinalysis disclosed a sugar content of 2 per cent. It was then suggested that this child, with her hepatomegaly, cataract, and melituria, might prove to be another case of galactemia.

Identification of the reducing substance in the urine was accordingly carried out. Baker's yeast did not ferment this substance, which gave a positive mucic acid test and yielded galactosazone crystals. It was therefore concluded that the sugar in the urine was galactose. The galactose tolerance test (Fig. 8) supported a diagnosis of galactemia. Further studies of the child's carbohydrate metabolism were undertaken and are described.

The remainder of the urinary findings were a mild albuminuria of 20 mg. per cent, occasional red and white blood cells, and granular casts; acetone and bile were absent. On the day after admission, a lumbar puncture was done because of the extreme irritability and

*Patient referred by Dr. Abel Lax.

the presence of a questionably full fontanel. This yielded spinal fluid under normal pressure, with no pleocytosis, a negative Pandy, and protein and chlorides within normal limits. The spinal fluid sugar was 161 mg. per cent, more than twice the normal value. (How much of this consisted of galactose was, unfortunately, not determined.) The total level of bilirubin in the plasma was 0.435 mg. per cent. The blood cholesterol was 91.9 mg. per cent. The total plasma proteins were 4.44 Gm. per 100 c.c., 3.90 of which were albumin and 0.54 globulin. Roentgenographs of the long bones demonstrated no decalcification.

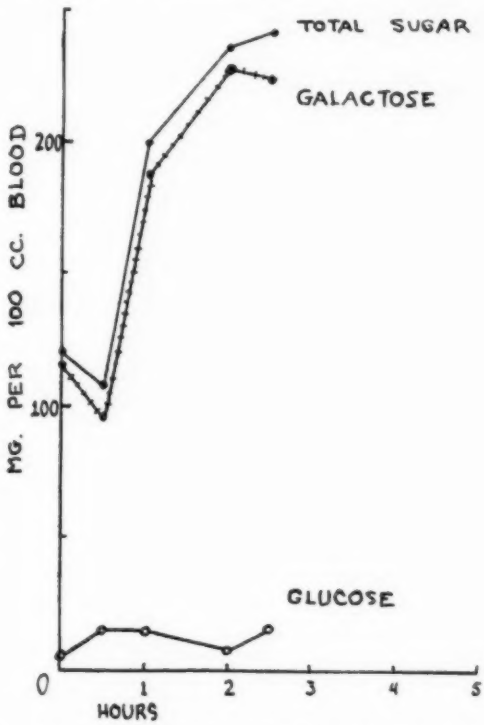

Fig. 8.—Values for total blood sugar, galactose, and glucose following ingestion of 1.75 Gm. of galactose per kilogram of body weight. (M. D. Oct. 6, 1944.)

Course.—Lactose was removed from the baby's diet three days after admission to hospital. At first she was fed bananas, egg yolk, Pablum, and a soybean flour formula. Because the latter was taken poorly it was replaced by a more acceptable suspension of washed milk curds in Ringer's solution sweetened with corn syrup. Sugar and albumin disappeared from the urine one week after the new regime was begun. Nevertheless the baby did not do well for some time afterwards. She had respiratory infections, particularly otitis media, accompanied by fever, diarrhea, and dehydration, requiring intensive chemotherapy, and the parenteral administration of fluids, including plasma and whole blood. When placed on a frame for the purpose of collecting a 24-hour specimen of urine, the baby rapidly developed decubitus ulcers on the thighs. These became deep and undermined and did not heal for several weeks. The baby's condition gradually improved, and she was discharged at the age of 5 months, weighing 8 pounds. The baby thrived at home on the same diet given in the hospital, to which were soon added puréed vegetables, beef, and liver. She had recurrent upper respiratory infection and otitis media, to which she remained very susceptible.

At 9½ months of age she was readmitted for further study. At this time she weighed 16 pounds, appeared very well nourished, had good color, could stand with support, and seemed to see quite well in spite of the cataracts which had perhaps regressed slightly, now appearing restricted to a 1.5 mm. central anterior opacity. The liver was somewhat smaller than on the first admission but still extended 5 cm. below the costal margin. Radiographs of the long bones still showed no decalcification. A prothrombin time of 17 seconds and a negative cephalin flocculation test demonstrated unimpaired liver function. The urinalysis was negative. There was no essential change in the blood chemistry, except that the total plasma protein had risen to 6.66 Gm. per 100 c.c. with the globulin dropping to 0.10 Gm. per 100 c.c., even lower than on the first examination. However, at one year of age the serum globulin had reached 1.62 Gm. per 100 c.c., a normal figure.

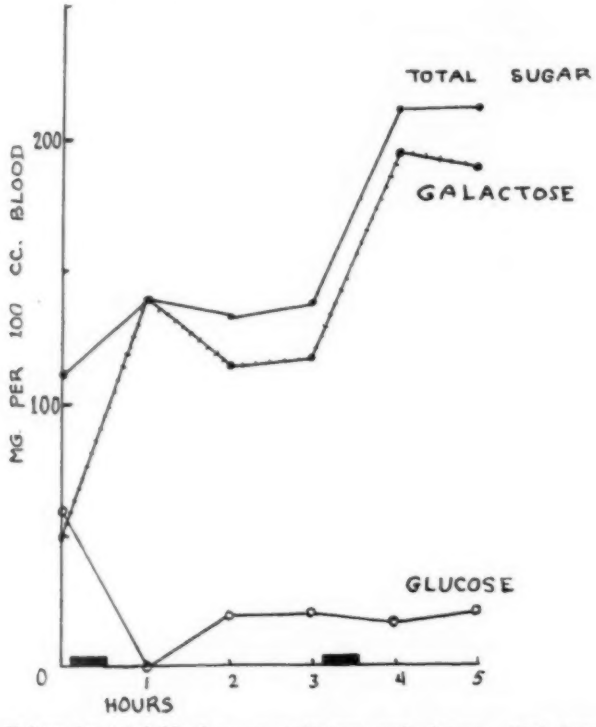

Fig. 9.—Values for total blood sugar, galactose, and glucose. Each heavy line along the abscissa represents the ingestion of a meal containing 200 c.c. of milk and 10 Gm. of lactose. (M. D. Oct. 17, 1944.)

Carbohydrate Studies.—A galactose tolerance test was carried out (Fig. 8). The greatly impaired tolerance shown confirmed the diagnosis of galactemia. The sugars were fractionated according to the method of Maclagan.[28] Here one noted an even greater depression of the blood glucose than was observed in Case 1. The high fasting level of galactose was evidently due to the fact that the baby received galactose test meals on the two previous days in technically unsuccessful attempts to study her tolerance and had not yet excreted all this galactose. The meaning of the initial drop in the galactose level preceding the rise is obscure. It was then demonstrated that when the child was given an ordinary diet containing milk, the blood was never free of galactose and always had a low glucose content (Fig. 9).

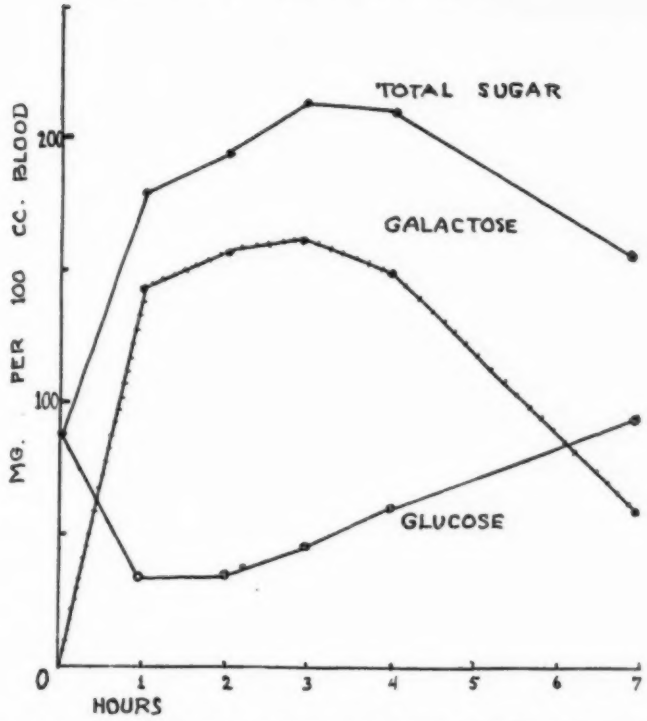

Fig. 10.—Values for total blood sugar, galactose, and glucose following ingestion of 1.75 Gm. galactose per kilogram of body weight. (M. D. April 10, 1945.)

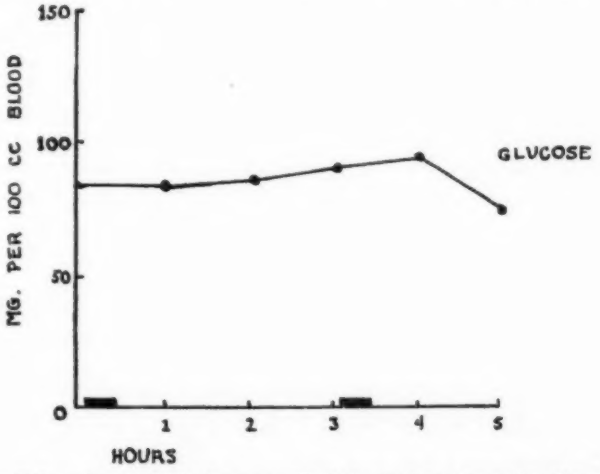

Fig. 11.—Values for total blood sugar. Each heavy line along the abscissa represents the ingestion of a lactose-free meal. The total blood sugar in these determinations consisted entirely of glucose, the presence of galactose having been excluded by fermentation. (M. D. May 25, 1945.)

On the second admission, four and one-half months later, the galactose tolerance test was substantially unchanged (Fig. 10). At this examination, the blood sugars were followed for seven hours after the ingestion of galactose; the galactose then having dropped to 60 mg. per cent, the blood glucose was mobilized to a level slightly higher than the fasting level. The level of blood glucose during the course of a day when the child received a lactose-free diet was then followed as a control to Fig. 9 (Fig. 11). This level proved to be significantly higher than when the child was receiving lactose. The glucose tolerance test was then shown to be within normal limits with glucose administered both orally and intravenously.[29] A quantity of galactose (0.2 Gm. per kilogram), calculated to raise the blood galactose to a level corresponding to that reached when milk was drunk, was then administered intravenously immediately preceding an oral glucose tolerance test, and later, preceding an intravenous glucose tolerance test. The intention was to find out which curve would be more profoundly depressed. The oral glucose curve was perhaps more affected than the intravenous glucose curve, but the point cannot be considered solidly established.

COMMENT

Two athreptic infants with hepatomegaly and cataracts were found to excrete a reducing substance in the urine. This reducing substance was identified as galactose. Feeding these children a lactose-free diet eliminated the galactosuria and permitted them to thrive at a satisfactory rate.

Usage thus far has labeled the disease with the name of galactemia, which we believe is not adequately connotative. Galactemia is not present when lactose is absent from the diet, but the metabolic error is always present. This error is the inability of the individual to metabolize galactose. Galactose cannot be utilized by conversion into glycogen but is apparently stored as such in the various organs and circulates as such in the blood stream whence it is excreted through the kidneys unchanged. A suitable name for such a disease would be galactose diabetes, just as diabetes mellitus indicates glucose diabetes. Each name should connote a train of symptoms and events characteristic of the respective metabolic disorder.

DISCUSSION

Galactose diabetes as seen in infants usually presents striking findings which should offer no difficulties in diagnosis. There is always failure to thrive and frequently intense hunger. Not only is lactose not utilized, but there is also good reason to believe that impediments to the utilization of glycogen exist at the same time and explain the hepatomegaly which is marked until lactose is removed from the diet. The tissues are saturated with galactose and the blood level for sugar, consisting chiefly of galactose, is high, and it would appear that the stimulus to glycogenolysis is wanting. Removal of lactose from the diet of such a patient relieves the intense hunger, permits growth, and empties the liver of the excess of stored glycogen. Blood sugar levels fall to normal limits and the sugar in the blood can be shown to be entirely glucose instead of nearly all galactose as when lactose is present in the diet.

The disease should be suspected and sought for whenever an infant manifests extreme hunger with failure to gain though the diet seems adequate, when there is hepatomegaly, cataract, and sluggish healing of damaged skin. Mental retardation was present in one of our cases and in several of those reported.

Fermentation, osazone, and mucic acid tests on the reducing substance in the urine will soon identify it as galactose. Ketosis is not a feature of this disease.

Here are presented two additional patients who could not utilize galactose. Since the important steps in the intermediate metabolism of this sugar, which make it available to the organism, take place in the liver, probably with the assistance of a specific enzyme system as suggested, one may justifiably consider the liver the site of the defect. The evidence implicating the liver is indirect. Massive hepatomegaly is a feature of all the cases reported to date, including our own; this may be only a manifestation of abnormal storage secondary to the primary defect and does not prove liver disease per se; this point will be further discussed. Goppert's[1] patient was icteric for the first eight months of his life. In one of the Baltimore cases, autopsy revealed a malformation of the liver with acinar grouping of the liver cells.[3b] In the case reported by Mason and Turner,[2] there was no positive evidence of liver dysfunction. Norman and Fashena[3] report some initial delay in bromsulfalein excretion in their case, but no other evidence of hepatic insufficiency. Mellinkoff and associates[5] report a reversible clinical picture resembling hepatic cirrhosis accompanying the galactemia. Our first patient had jaundice lasting about three weeks in the neonatal period; our second patient showed no liver disturbance. It would appear that this anomaly may occur either as part of the picture of hepatic insufficiency or as a single primary defect of liver function which we assume to be located in the specific enzyme system which converts galactose. We feel that the two cases presented here fall into the latter class.

It is noted that all cases so far reported, except our second case, show an elevation of blood bilirubin; but it is the indirect fraction only which is elevated, the direct being consistently normal. This feature has not hitherto been explained but certainly does not suggest liver damage; it may be correlated with the frequent finding of anemia as evidence of hemolysis. We have no explanation for the occurrence of a hemolytic anemia in this condition.

Mason and Turner[2] pointed out that the enormous disturbance of nutrition occurring in these children was difficult to account for on a basis of deprivation of the organism of galactose, which amounts to so small a proportion of the expected carbohydrate intake. They postulated that the mechanism for lowering the blood sugar by its storage in the liver as glycogen operates in response to an elevation, not of the blood glucose alone, but of the total blood sugar; but it can act in these cases on glucose only because galactose cannot be converted. This results in an excessively low level of blood glucose. They demonstrated such a continuously low blood glucose in their patient when his diet contained lactose, and they attributed his failure of nutrition to this relative glucose starvation. We are in agreement with this view and have demonstrated in both of our patients a striking hypoglycemia accompanying the hypergalactosemia produced by lactose feedings, the blood glucose reaching zero on one occasion.

If this view of the pathogenesis is correct, the liver enlargement may well be due, as Mason and Turner[2] suggest, to the excessive formation and storage of glycogen in response to the hypergalactosemia. If so, one would expect the hepatomegaly to disappear when lactose is removed from the diet. In our cases.

the size of the liver decreased rather slowly, remaining somewhat above normal after six months of treatment in our second patient and after five years in our first patient. This suggests that glycogen storage may be only partly to blame. Norman and Fashena[3] suggested that storage of something else might occur; fat for instance, or even galactose. The fatty infiltration such as occurs in relative carbohydrate starvation should also disappear more rapidly. It seems entirely possible that some storage of galactose as such does occur, for we found galactose in the urine and blood as late as one week following removal of lactose from the diet. This, of course, might indicate storage in the tissues rather than in the liver; but Norman and Fashena noticed a sudden increase in the size of the liver the day after a large dose of galactose was given. However, galactose storage is equally unsatisfactory as an explanation of the hepatomegaly remaining one year later. The absence of any signs of hepatic insufficiency in the cases under prolonged treatment makes it unlikely that fibrotic changes in the liver may have supervened. Liver biopsy is not available as a means of investigating this problem; for, before good nutrition has been established by a lactose-free regime, it is a hazardous procedure, and after this has been established, it would no longer give the necessary information. Thus the full nature of the hepatomegaly remains unexplained.

It is altogether likely that the blood glucose is depressed in the presence of hypergalactosemia through the mechanism of glycogen formation in the liver, as suggested by Mason and Turner,[2] and discussed herein. Yet we may consider the possibility of another mechanism, perhaps accessory. The rate of absorption of glucose is slowed by the simultaneous absorption of galactose, the intestinal mucosa being able to accept only a limited load. During the ingestion of milk, the quantity of galactose made available would be too small to affect appreciably the absorption of glucose derived from the other food taken. But since the diffusion gradient of monosaccharide from the mucosal cells into the portal blood must be lessened by a hypergalactosemia, it is reasonable to suppose that the rate of absorption of glucose could be slowed by this means (that is, if it is the level of total sugar, and not merely of glucose, which affects the gradient of glucose from the mucosa into the portal blood as it does from the intestine into the mucosa, a point not yet determined experimentally). Some of the early experiments,[9] working with a single sugar, showed that one could depress glucose absorption in dogs by raising the glucose concentration of the blood. Verzar,[9] however, has raised the blood concentration of glucose in rabbits to 520 mg. per cent without affecting the absorption of glucose. In our second patient, the depression of blood glucose by intravenous galatose is relatively greater when glucose is given orally than when it is given intravenously; this finding is compatible with the suggestion that galactosemia interferes with the absorption of glucose from the intestine. Further investigation of this point is required.

Whether we are dealing with blocked absorption of glucose, or solely with hepatic hoarding of glucose with deprivation of the tissues, the net effect of hypergalactosemia is one of glucose starvation. Norman and Fashena[3] pointed out that the glucose tolerance curve of their patient was at first similar to a curve obtained during starvation, and demonstrated the gradual return of the

glucose tolerance to normal with treatment. We observed the same phenomenon in our first case. It is possible that this tissue starvation is responsible for such features as the intractable pressure ulcers in our second patient, and the constant finding of albuminuria; although a direct toxic effect of excess galactose in the tissues cannot be excluded.

Mental retardation has been observed in the patients described by Goppert,[1] and Mason and Turner,[2] and in our first patient. It is not present in the patient described by Norman and Fashena[3] and in our second patient. It was notably in the latter two that removal of lactose from the diet was effected early, before the twentieth week of life. This suggests that the mental retardation is not an associated congenital defect, but rather a result of the interference by the galactosemia with the supply of glucose to brain tissue as well as to other body tissues; or perhaps there is a direct toxic effect of excess galactose on brain tissue. There would seem to be no disturbance of myelinization as a result of the therapeutic withdrawal of exogenous galactose, judging from the satisfactory neuromuscular development of our second patient.

Although galactose is not converted into glycogen it seems able to prevent the appearance of hypoglycemic symptoms. In one experiment (Fig. 11) when a milk meal enriched with added lactose was fed, glucose apparently disappeared completely from the circulating blood within one hour and the total blood sugar of about 140 mg. per cent consisted entirely of galactose. Yet no symptoms of hypoglycemia appeared. One patient did, however, have a brief convulsion during the course of a carbohydrate-insulin curve, at a time when the blood glucose was 43 mg. per cent and the galactose 90 mg. per cent. We have no explanation of this to offer. (This curve is not reproduced here because it was incomplete.) This brings up the interesting question of the nature of hypoglycemic reactions. We may assume that galactose can be utilized directly by nerve tissue, perhaps by a mechanism which involves the intermediate metabolism of the cerebrosides or lacactolipids, and thus protects nerve tissue from damage in periods of glucose depletion.

Certain other findings are difficult to explain. Both of our patients repeatedly showed unusually low values for serum globulin at first, but normal values later. This was not so in the other cases reported. We do not know its significance. The susceptibility of both of these infants to infections may be on this basis. We cannot explain the osteoporosis present in all the reported cases and in one of our cases.

Treatment of these children consists essentially of the withdrawal of milk from their diet. The substitute most commonly used has been a formula prepared from soybean flour, with other foods and vitamins suitable to the age period. The Sobee formula was taken well by our first patient but not by our second. For this reason the simple expedient of using washed milk curds resuspended in Ringer's solution sweetened by corn syrup was successfully tried. Goppert[1] used a similar feeding for his patient. It may be noted that whereas any milk is injurious to these infants, human milk is more so than cow's milk because of its higher lactose content.

It is possible that the galactose tolerance of these children may improve over a period of time. Thus the total blood sugar curve obtained in Case 1 after a galactose test meal reached 588 mg. per cent the first time (Fig. 3) and only 250 mg. per cent seven months later; five years later it reached 200 mg. per cent (Fig. 7). Curves in Case 2 did not change appreciably in six months.

It is of interest to find in one of the first articles by Mitchell and Dodge[16] on galactose cataract, a reference to Mason and Turner's[2] presentation of a case of galactemia. In view of the infallible production of cataract in experimental animals by the feeding of galactose in quantities sufficient to raise the blood galactose level appreciably, the conclusion may justifiably be drawn that the hypergalactosemia in these children causes the cataract. The objection has been that in both of these cases the cataract has been chiefly nuclear, and nuclear cataract is generally considered to form before the development of the lens nucleus has been completed, that is by the third month of fetal life. A normal galactose tolerance test on the mother of the patient in Case 2 ruled out the exposure of this infant to a high concentration of blood galactose during fetal life. This mother's story is that the cataract was not present at birth. Finally the production of nuclear cataract in young rats, by high blood levels of galactose in postnatal life, is at least strong, suggestive evidence that cataract may occur in this way in human young. It is certainly significant that the incidence of cataract in cases of galactemia has been to date at least 50 per cent.

The experimental finding that galactose-produced cataract regressed in part, on withdrawal of galactose,[24] is of interest here. The patient described by Mason and Turner had cataracts and has undergone operation for them.[31] The cataracts exhibited by a patient with galactosemia studied by Bruck and Rapoport[6] resolved after galactose was removed from the diet. Our first patient's cataracts regressed only slightly over a six-year period of observation, at the end of which time operation was performed. Our second patient's cataracts have regressed very little after nine months of observation.

SUMMARY AND CONCLUSIONS

1. Two infants in whom occurred the syndrome of hepatomegaly, inanition, cataract, galactosuria, and galactosemia are presented.

2. This anomaly of galactose metabolism is discussed.

3. The cataract in this condition is related to experimentally produced galactose cataract, the pathogenesis of which is reviewed.

4. Therapeutic control of this condition is readily effected by a lactose-free diet.

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IMMUNIZATION WITH TETANUS TOXOID

The Persistence of Antitoxin and the Effect of Stimulating Doses of Alum-Precipitated Tetanus Toxoid After a Five-Year Period

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ACTIVE immunization against tetanus is now recognized as a routine procedure in pediatric practice. The antitoxin response to two injections of tetanus toxoid alone or in combination with diphtheria toxoid has been most gratifying. However, few data are given on the persistence of antitoxin in immunized individuals and the antitoxin response after several years to the injection of varying amounts of tetanus toxoid.

In 1936, we reported[1] the serum antitoxin content in ninety-four children following immunization with two doses of 1 c.c. each of alum-precipitated tetanus toxoid with an interval of seventy-three days. The toxoid used had a minimum toxocity of 15,000 minimum lethal doses per cubic centimeter. Serum antitoxin levels were determined forty-five days after the first injection and fifty-four days after the second injection. The methods of testing for serum antitoxin have been previously described.[1] The results of this study are summarized in Table I. After the first injection, 16.3 per cent of the children had an antitoxin level of 0.1 unit per cubic centimeter* and after the second injection all children had 0.1 or more units per cubic centimeter, while the majority had from 0.25 to 1 unit of antitoxin per cubic centimeter of serum. These data are in agreement with other published reports.[2-9] During the ensuing five years the children were tested at intervals and were given varying amounts of alum-precipitated tetanus toxoid subcutaneously or intradermally.

Persistence of Antitoxin After Primary Immunization.—Thirty-three children (Table II) were tested for serum antitoxin one year after the primary immunization. At that time the antitoxin level was 0.01 unit in three individuals, 0.1 unit or more per cubic centimeter in twenty, and ten of the group had more than 0.25 unit per cubic centimeter. After thirty months the sera of another group of twenty-nine individuals were titrated. Sixteen of these had 0.01 unit per cubic centimeter, ten had 0.1 unit, and only three 0.25 unit of antitoxin per cubic centimeter. The third group of fifteen individuals, tested five years after the original two doses of toxoid, showed a lower titer of antitoxin. One individual had less than 0.01 unit per cubic centimeter,

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*No serum antitoxin titrations were done before the primary immunization since tetanus antitoxin is not found in appreciable amounts in the serum of nonimmunized individuals. The protective level of 0.1 c.c. was taken, though this probably is a higher level than is necessary for complete protection. Sneath[2] found that individuals given a prophylactic dose of 1,500 units of tetanus antitoxin had maximum of 0.1 to 0.25 unit per cubic centimeter of blood serum after one week.

TABLE I. UNITS OF TETANUS ANTITOXIN PRODUCED IN BLOOD SERA BY ALUM-PRECIPITATED TETANUS TOXOID

UNIT	NO. OF CHILDREN	PER CENT
Forty-five days after injection of 1 c.c. toxoid		
Less than 0 01	2	2.2
0.01	75	81.5
0.1*	13	14.1
0.25	2	2 2
Total	92	
Fifty-four days after second injection of 1 c.c. and 127 days after first		
0.1*	5	5.8
0.25	18	21.2
0.5	26	30.6
1	31	36.5
2	3	3.5
3-5	2	2.4
Total	85	

*Protective level.

TABLE II. PERSISTENCE OF SERUM ANTITOXIN IN CHILDREN WHO RECEIVED TWO DOSES ONE CUBIC CENTIMETER ALUM-PRECIPITATED TETANUS TOXOID WITH AN INTERVAL OF SEVENTY-THREE DAYS

UNITS OF ANTITOXIN PER C.C. OF SERUM	TIME AFTER THE LAST INJECTION OF TETANUS TOXOID			
	54 DAYS	12 MONTHS	30 MONTHS	60 MONTHS
3-5	2			
2	3			
1	31			
0.5	26	3		
0 25	18	7	3	
0.1	5	20	10	2
0.01		3	16	12
Less than 0.01				1
Total Number of Children	85	33	29	15

twelve had 0.01, and only two had 0.1 unit of antitoxin per cubic centimeter. Thus there was a gradual decrease in titer so that the majority of individuals were below 0.1 unit in thirty months, and thirteen of fifteen were below this level at sixty months.

The Effect of a Stimulating Dose of 1 c.c. at the End of One Year.—Thirty-five children were given 1 c.c. of alum-precipitated toxoid one year after completion of the basic immunization. The response (Table III) was rapid and marked. Before stimulation, twenty-three of thirty-three children had 0.1 unit or less per cubic centimeter, and no child had more than 0.5 unit per cubic centimeter. One week after stimulation, all had 2 units or more per

TABLE III. EFFECT OF STIMULATING DOSE OF 1 C.C. ALUM-PRECIPITATED TETANUS TOXOID AFTER ONE YEAR

TITRATIONS DONE ONE WEEK AFTER STIMULATING DOSE

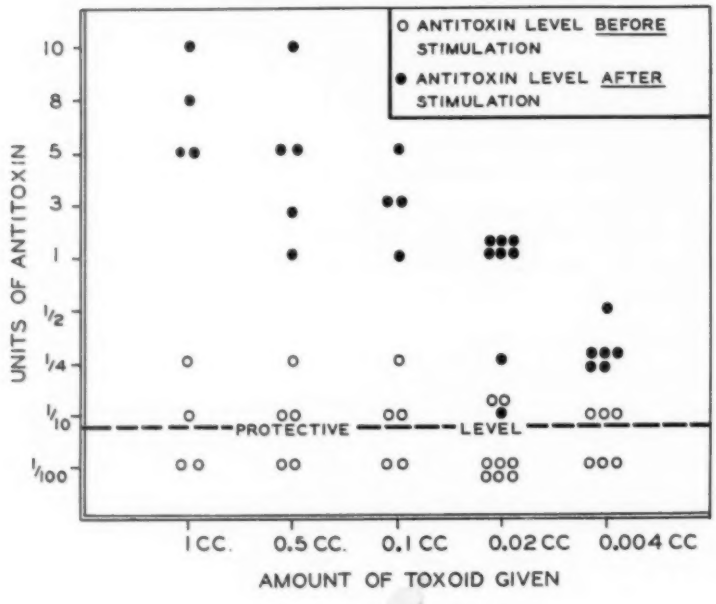
BEFORE STIMULATION		AFTER STIMULATION	
UNITS OF ANTITOXIN PER C.C. OF SERUM	NO. OF CHILDREN	UNITS OF ANTITOXIN PER C.C. OF SERUM	NO. OF CHILDREN
0.01+	3	2	2
0.1+	20	4	8
0.25+	7	6	14
0.5+	3	10	9
		15	2

cubic centimeter, and twenty-five of thirty-five children had 6 or more units per cubic centimeter. Titrations were again done on nine of this group eighteen months after the stimulating dose when the serum levels varied from 0.1 to 1 unit of antitoxin per cubic centimeter.

The Effect of Stimulating Doses After Two and One-half Years.—Chart I shows the stimulating effect of varying amounts of tetanus toxoid injected subcutaneously thirty months after the basic immunization. Four individuals who had from 0.01 to 0.25 unit of antitoxin per cubic centimeter when given 1 c.c. of toxoid responded in one week with a level of 5-10 units of antitoxin per cubic centimeter. When 0.5 c.c. of toxoid was given to five individuals with similar levels, the rise was to 1-10 units per cubic centimeter with a greater spread in the response. When 0.1 c.c. was given to five individuals, the rise was to 1-5 units per cubic centimeter. Eight individuals were given 0.02 c.c. of toxoid with a rise from 0.01-0.1 to 0.1-1 unit per cubic centimeter. When 0.004 was given to six individuals, the rise was from 0.01-0.1 to 0.25-0.5 unit per cubic centimeter. It is evident that while adequate levels may be reached with 0.004 c.c. of toxoid, 0.1 c.c. is probably the smallest practical "booster" dose. Thus the usual stimulating dose of 1 c.c. (often using a toxoid which is twice as potent) would seem to be entirely unnecessary as well as more dangerous so far as reactions are concerned.

CHART I

RESPONSE TO INJECTION OF VARYING AMOUNTS OF ALUM PRECIPITATED TETANUS TOXOID 30 MONTHS AFTER THE PRIMARY IMMUNIZATION

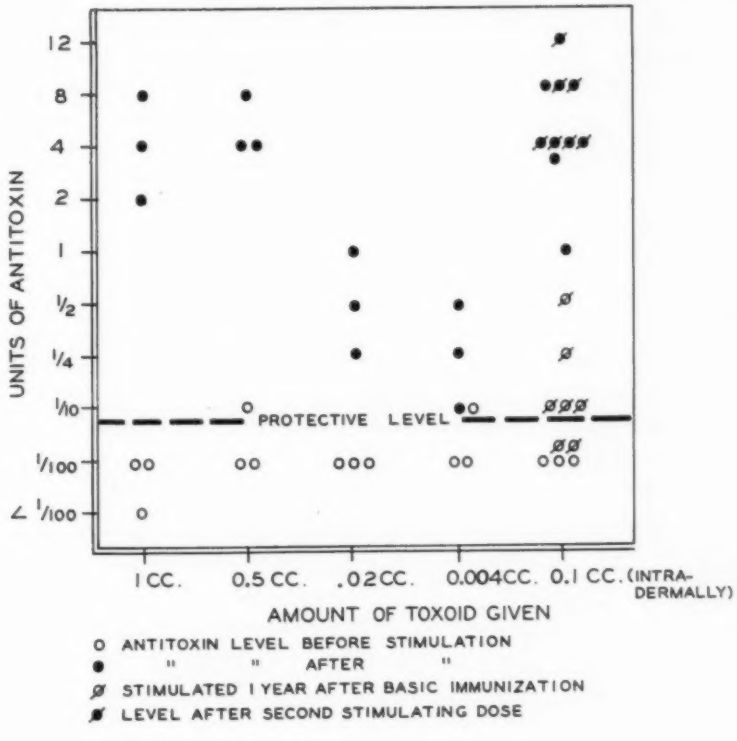


The Effect of Subcutaneous and Intradermal Stimulating Doses After Five Years.—Chart II shows the effect of subcutaneous and intradermal injections of tetanus toxoid in varying amounts five years after the basic immunization. One individual with less than 0.01 unit of antitoxin per cubic centimeter, and two with 0.01 per cubic centimeter were given 1 c.c. of alum-precipitated toxoid subcutaneously. The rise was to 2-8 units antitoxin per cubic centimeter. Three individuals with 0.01-0.1 unit per cubic centimeter were given 0.5 c.c. of toxoid resulting in a rise to 4-8 units per cubic centimeter, while three with 0.01 unit per cubic centimeter showed a rise to 0.25-1 unit per cubic centimeter when stimulated with 0.02 c.c. of toxoid. Administration of .004 c.c. of toxoid resulted in a smaller rise to 0.1-0.5 unit per cubic centimeter.

The effect of intradermal administration of 0.1 c.c. of alum-precipitated tetanus toxoid after five years (Chart II, Column 5) was determined in 10 individuals. Sera of five children who had been given a stimulating dose of 1 c.c. of alum-precipitated toxoid one year after the basic immunization had

CHART II

RESPONSE TO INJECTION OF VARYING AMOUNTS OF ALUM PRECIPITATED TETANUS TOXOID 5 YEARS AFTER THE PRIMARY IMMUNIZATION



levels varying from 0.01 to 0.5 unit per cubic centimeter. One week after they received 0.1 c.c. toxoid intradermally the level was 4-12 units antitoxin per cubic centimeter. Three individuals who had not been stimulated had 0.01 unit per cubic centimeter and had rises to 1, 4, and 8 units per cubic centimeter. Thus it would seem from these figures that 0.1 c.c. toxoid intradermally is perhaps as valuable as 0.5 c.c. subcutaneously.

DISCUSSION

The marked increase in serum antitoxin content resulting from the injection of 0.004 c.c. of toxoid subcutaneously five years after the original immunization would lead one to believe that the stimulating dose may be unnecessary, although caution dictates its use. When the basic immunity has been well established, the presence of actual infection should cause the immunized individual to respond with rapid antitoxin formation. The response in our series was rapid and adequate, regardless of the level to which the antitoxin had fallen in the periods since primary immunization.

This series was done entirely on Negro children. It has been stated occasionally that the Negro reacts with greater antitoxin formation than does the white child. If this is true it may explain the higher antitoxin levels obtained by us than by other workers. The ages at the time of the primary immunization varied from 3 to 8 years. The children were almost equally divided as to sex. No difference in antitoxin response was noted for either age or sex.

The interval of two and one-half months between the primary doses resulted in an adequate response. Bigler and Werner[8] report that the optimum interval between injections is three months.

Reactions were not severe in any of the individuals. All of those of school age were able to continue in school. About 10 per cent of the children complained of soreness at the site of injection. Twenty-four hours following the intracutaneous injection of 0.1 c.c. of alum-precipitated toxoid an area of erythema varying from 2 to 6 cm. was noted. A small nodule was formed which disappeared in about four weeks. No abscess formation or necrosis occurred. One would expect more severe skin reactions in white children so that plain tetanus toxoid probably would be better as a routine intradermal stimulating substance.

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ESTABLISHMENT OF A TRANSFUSION CLINIC

Treatment of Mediterranean Anemia in the Outpatient Department

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THE successful management of severe Mediterranean (Cooley's) anemia requires frequent blood transfusions. It is only since the introduction of this therapeutic agent that a few children with this illness have survived to and beyond adolescence. Atkinson[1] reported two cases, siblings, 17 and 20 years old, who were followed from early childhood. They had typical bone and blood findings of Cooley's anemia. One child did not require transfusions and the hemoglobin level remained approximately 8 Gm. per 100 c.c. of blood. Aside from a late menarche she was apparently normal. The other sibling, a boy, had a more severe anemia which appeared to be benefited by splenectomy. He required one subsequent hospital admission and remained well thereafter. Smith[2] describes a patient who was then 23 years old. He had characteristic findings of Cooley's anemia. Prior to 1929 he had required five admissions to the hospital, but since that time his hemoglobin had been maintained at approximately 8 Gm. per 100 c.c. of blood. The disease in these patients was not comparable in severity with the cases to be described. Irrespective of the apparent severity of the disease there is always the possibility of spontaneous remissions, an outcome which has been observed in a few cases followed at the New York Hospital. It is, therefore, essential that all efforts be made to keep alive patients with this illness.

SUBJECTS

Six children with the severe form of Cooley's anemia have been followed at the New York Hospital for several years. They vary in age from 2 to 10 years. Prior to the establishment of the transfusion clinic these children required frequent hospitalizations for transfusion and other illnesses which often accompanied the anemia. These illnesses usually involved the upper or lower respiratory tract, but cardiac complications were not uncommon. Reference to Table I reveals the frequent number of hospitalizations required by the children: 7 for the youngest child, and 45 for the oldest child. The total number of patient-days in the hospital was 1,774; the total number of transfusions was 651, consisting of 101,800 c.c. of blood. It may be noted that hospital admissions were becoming more frequent as the patients grew older. Any normal continuity of home and school life was impossible.

In March, 1944 (seventeen months before time of writing), a transfusion clinic was established to treat these patients on an ambulatory basis. Initially, only two children were accepted for the clinic. However in November, 1944

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TABLE I. HOSPITAL ADMISSIONS, TRANSFUSIONS, AND ILLNESSES PRIOR TO ESTABLISHMENT OF THE TRANSFUSION CLINIC

CASE	AGE (YR.)	ADMISSIONS	DAYS IN HOSPITAL	ADMISSIONS IN YEAR PRIOR TO CLINIC TREATMENT	TRANSFUSIONS	C.C. OF BLOOD	SEVERE ILLNESSES
1	8	12	143	5	64	10,300	8
2	6	11	170	4	70	11,500	10
3	6	18	220	8	111	19,500	5
4	7	27	509	5	145	22,000	6
5	2	7	75	6	37	4,500	2
6	10	45	657	5	224	34,000	19
Total		120	1,774	33	651	101,800	50

TABLE II. SUMMARY OF OUTPATIENT DEPARTMENT THERAPY

CASE	MONTHS IN O.P.D.	TRANSFUSIONS	C.C. OF BLOOD
1	16½	52	18,350
2	16½	48	16,400
3	8½	23	8,700
4	8½	21	8,250
5	5	16	3,100
6	5	14	4,900
Total		174	59,800

(eight months before time of writing), two other children were added to the group. In February, 1945 (six months before time of writing), the group of six was completed. Table II shows the number of transfusions and amount of blood utilized since the establishment of the clinic. Fig. 1 is the graphic representation of hemoglobin levels in Case 1. The first part of the chart reveals the large irregular changes in hemoglobin value with the levels falling to 5 or 6 Gm. and then being restored by hospital transfusion. The second portion of

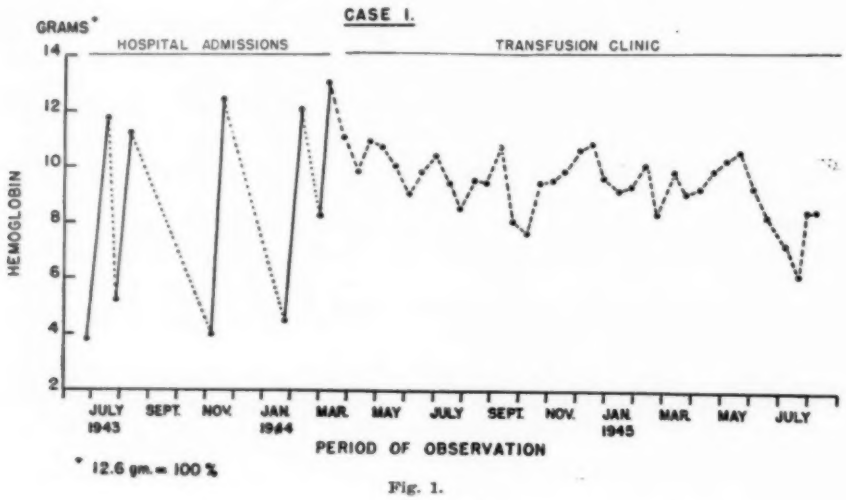

Fig. 1.

the graph represents a year and a half of experience in the transfusion clinic with the hemoglobin values stabilized around 9 Gm. Except for minor respiratory illnesses the entire group has been well, required no hospitalization, and has been regular in school attendance.

METHODS AND MATERIALS

The equipment consists of a transfusion set, sterile gauze, medicine glass, tourniquet, and adhesive tape. The transfusion set is equipped with a three-way stopcock at the junction of syringe and needle, so blood can be either pumped in or allowed to flow by gravity. Type O red blood cells obtained from the Red Cross Blood Donor Center are used exclusively. For the first six months the red cells were suspended in saline and subsequently in 10 per cent corn syrup.

The patients arrive at noon when blood is drawn for counts and cross-matching. The blood studies consist of hemoglobin determination, red blood cell count, and volume of packed red cells; occasionally a white count and differential are done. When the clinic was first established, 250 c.c. of blood were given each child every week. It is possible to prolong the interval to every two weeks if from 450 to 500 c.c. of blood are used. This is now the routine except in the case of a 2-year-old boy who receives 250 c.c. every two weeks. Approximately one hour is allowed for each transfusion to be completed.

Following the transfusion the children are permitted to play quietly. If reactions occur, they take place within one hour following transfusion. Therefore, temperatures are taken one hour after treatment and if they are not elevated above 39° C. (103° F.) and there is no severe reaction, the patients may leave. It has been unnecessary to keep any patient longer than two hours after transfusion.

TRANSFUSION REACTIONS

Transfusion reactions have been of frequent occurrence and have been completely unpredictable and inexplicable. They may be grouped as follows:

a. Fever, chills, and headache, usually mild and transient, are often relieved by acetylsalicylic acid.

b. Asthma and urticaria occurred twice each and responded to adrenalin.

c. Hemolysis—one severe hemolytic reaction accompanied by deep jaundice and nausea was treated by bed rest and diet. A few milder attacks have occurred.

d. Local pain along the course of the vein occurs in a few patients if the blood is injected rapidly.

None of the reactions have been severe enough to require hospitalization or discontinuation of outpatient department therapy.

CASE HISTORIES

CASE 1.—R. P. was a 7-year-old girl of Italian ancestry whose anemia was first detected in 1939. The anemia is associated with hepatosplenomegaly and typical x-ray and blood findings of Cooley's anemia. From 1939, to March, 1944, she was hospitalized twelve times;

five of these admissions occurred in the year prior to establishment of this clinic. She spent 143 days in the hospital and received sixty-four transfusions consisting of 10,000 c.c. of blood.

On March 10, 1944, transfusions in the clinic were started. At this time the patient's hemoglobin was 13 Gm. per 100 c.c. of blood, red cell count was 3.8 million per 100 c.c., and volume of packed red cells was 30. She has been transfused every one or two weeks since then and has had a total of fifty-two transfusions consisting of 18,350 c.c. of suspended red cells. The hemoglobin at the time of writing was 8.4 Gm.; red cell count, 3.9 million; and volume of packed red cells, 29. She experienced occasional febrile responses, slight headache, and chills following transfusions. Her health has been good except for a few mild respiratory infections.

CASE 2.—J. P. (brother of R. P.) was a 6-year-old boy who was first seen at the New York Hospital when 4 months old. Hepatosplenomegaly was found and blood count revealed a hemoglobin value of 8 Gm. per 100 c.c. Blood smear showed stipple, target and nucleated red blood cells. The first hospital admission was in February, 1939, because of weakness and a severe upper respiratory infection. He has had ten subsequent admissions, four of which were in the year previous to the establishment of the transfusion clinic. Severe respiratory infections have always accompanied this boy's anemia, and on the last nine admissions he required sulfonamide therapy. He was hospitalized for a total of 170 days and received 11,000 c.c. of blood in seventy transfusions.

Outpatient department transfusions were started March 17, 1944. The blood count was hemoglobin 11.8 Gm. per 100 c.c. of blood; red cell count, 3.7 million per 100 c.c.; and volume of packed red cells was 34. He has since been transfused forty-eight times and received 16,400 c.c. of suspended red cells. The hemoglobin has varied from 8 to 12 Gm. per 100 c.c. of blood. The last determinations showed hemoglobin, 8.6 Gm.; red blood cell count, 3.3 million; and volume of packed red cells, 29. Following transfusions he has had some febrile reactions; on two occasions he had urticaria; and he had one severe asthmatic attack. His health, since March, 1944, has been good except for mild respiratory infections.

CASE 3.—S. S. was a 7-year-old girl of Greek extraction. Anemia was first noted at 10 months of age, but she did not require hospitalization until 3 years of age. At that time the hemoglobin was 8.5 Gm. per 100 c.c., and blood smear and bone changes were typical of Cooley's anemia. She had an enlarged liver and spleen. This first admission was associated with a peritonsillar abscess. Since then she has had seventeen admissions, most of which have been uncomplicated. She received 19,500 c.c. of blood in 116 transfusions.

This patient's first outpatient department transfusion was on Nov. 10, 1944. At this time the hemoglobin was 10 Gm. per 100 c.c., red cell count was 3.6 million, and volume of packed red cells was 26. In the past eight months she has received twenty-three transfusions totaling 8,700 c.c. of blood. She has had occasional febrile reactions and chills. The last hemoglobin determination was 8.8 Gm.; red cell count, 2.8 million; and volume of packed red cells, 31. During the year before clinic transfusions were begun the patient was hospitalized eight times. In the eight months since the patient joined the group her health has been good.

CASE 4.—J. F. was a 7-year-old boy of Italian parentage. He was first seen at the New York Hospital at age of 3 months because of bronchopneumonia and otitis media. The next admission was one month later because of pneumonia. He was extremely ill and was discovered to have Cooley's anemia. A splenectomy was performed when he was one year old. Since then he has remained fairly well except for the recurring anemia. He has had twenty-seven admissions to the hospital totaling 509 days and has received 22,000 c.c. of blood in 145 transfusions.

This patient started attending the transfusion clinic Nov. 10, 1944, at which time the hemoglobin was 10 Gm. per 100 c.c. of blood, red cell count was 3.3 million, and volume of packed red cells was 30. Following the first transfusion he had fever and a slight chill; the following day he became markedly jaundiced. He remained deeply icteric for two weeks but did not require hospitalization. Subsequent transfusions have been uneventful. He has received twenty-one transfusions consisting of 8,250 c.c. of red cells. The last hemoglobin

determination was 8.6 Gm., red cell count was 3.2 million, and volume of packed cells was 31. The year before attending this clinic the patient required hospitalization five times; this year he has been in excellent health.

CASE 5.—D. B., a 2-year-old Italian boy, was admitted to the New York Hospital because of pallor and hepatosplenomegaly, when 4 months old. Blood findings were consistent with the diagnosis of Cooley's anemia, but x-rays of skull and long bones were normal and have remained so. He has had six subsequent hospitalizations during which time he received seventy-five transfusions of 4,500 c.c. He was added to the outpatient group Feb. 2, 1945. Since then he has had sixteen transfusions consisting of 3,100 c.c. of blood. He has had no reactions to transfusions but has presented the mechanical problem of finding suitable veins. The blood on last determination showed hemoglobin, 9.4 Gm. per 100 c.c.; red cell count, 3.2 million; and volume of packed red cells, 28.

CASE 6.—I. C. was 10 years old. Her parents were Sicilians. She had a twin brother who had the trait but not the active form of Cooley's anemia. Pallor was noted at birth, and a diagnosis of Cooley's anemia was established when she was 17 months old. She also has a complete situs inversus. She has had forty-five hospital admissions; five of these were in the year prior to start of clinic therapy. During the early years she required hospitalization approximately every seven weeks. She had a splenectomy when 3 years old and has required transfusions about every eleven weeks since. She has had many severe respiratory infections associated with the anemia and has also had one attack of pericarditis with effusion. When she becomes anemic she develops severe headaches and chest pain. She has spent 657 days in our hospital and received 34,000 c.c. of blood.

The patient started clinic transfusions on Feb. 23, 1945. At this time the hemoglobin was 9.8 Gm. per 100 c.c., red cell count was 3.9 million, and volume of packed red cells was 32. She has had fourteen transfusions consisting of 4,900 c.c. of blood. The last hemoglobin determination was 9.2 Gm.; red cell count, 2.9 million; and volume of packed cells was 30. She has always had severe headaches and chills following transfusions; these have not been so severe in the outpatient department.

COMMENTS

Treatment of our patients with Cooley's anemia in the outpatient department was undertaken for several reasons:

1. Repeated hospitalizations interfere with the normal continuity of home and school life.

2. Sustenance of adequate blood levels is physiologically more sound than replenishment of blood at irregular intervals.

3. Reduction in hospital expense.

4. Better utilization of available bed space in a teaching institution.

With the establishment by the American Red Cross of centers for collecting blood plasma, residual red blood cells have been obtainable in abundance. These cells are reportedly equal in therapeutic efficacy to whole blood[3] in treating severe anemias, and their use eliminates the necessity for obtaining blood donors. It is only because of the ready availability of these cells that the outpatient department transfusion clinic has been feasible. The American Red Cross, with the end of World War II, has temporarily abandoned its project of blood collection.* This is unfortunate, as the red cells can be used to treat many

*Since August, 1945, we have had seven months' experience using only whole bank blood and we find this more satisfactory in maintaining good blood levels.

forms of anemia which must once more be treated with whole blood. It is hoped that the blood bank will be re-established as a permanent peace-time institution.

SUMMARY

1. The establishment of an outpatient transfusion clinic is described.

2. Type O washed red blood cells obtained from the Red Cross Blood Donor Center are used exclusively. These are supplied free and are essential to the maintenance of the clinic. It is to be hoped that these cells will be available in the postwar period.

3. The case histories of six patients with severe Mediterranean anemia are presented. These patients formerly had many serious illnesses and required frequent hospitalizations. Since attending the transfusion clinic they have been in good health, and the five older children have attended school regularly for the first time. The first two patients admitted to the clinic have now been followed for seventeen months.

4. An outpatient clinic of the type described can probably be organized to treat any form of chronic anemia requiring repeated interval transfusions.

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DOES MILK BETWEEN MEALS HAMPER THE APPETITE OR FOOD INTAKE OF THE CHILD?

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THE studies here described owe their motivation to a thesis laid down before the American Pediatric Society in 1940, by one of its senior members, to the effect that: "Milk requires 3 to 3½ hours for complete gastric digestion. . . To give it at 10:30 [in school] and then send the child home for lunch at 12 violates the rules of physiology, dietetics and common sense. Experience shows that the appetite for lunch may be much impaired." That "routine feeding of milk midway between meals is certainly not advisable," was concurred in by two discussors, whereas only one dissent was mildly voiced: "There are great individual differences in the ability of children to take it and get along well on it."[1]

Is it truly unwise to offer children, as is so often done in schools and homes, a glass of milk in mid-morning or mid-afternoon? In studies by the writer on the physiology of milk digestion during childhood,[2] no appetite-impairing effect from milk had been noted. The same studies had indicated that following the drinking of 8 ounces of milk the gastric emptying time may range from 50 to 170 minutes; the mean of 122 experiments was almost exactly 120 minutes.

It seemed worth while, therefore, to determine more directly whether milk impairs the appetite. A controlled series of feeding experiments could be expected to yield more reliable information than would be gained by sporadic interviews of random patients and their mothers—which kind of data, partially subjective, appeared to have served as the bases for the opinions just cited.

Available for testing purposes was the same large group of children, recuperating from rheumatic fever in a rest home but otherwise well. All had been through one or more episodes of acute illness in the preceding year or two, necessitating complete bed rest for weeks or months, but were now in the recovery phase, free from fever and active symptoms, and ambulant for the greater part of the day. Institutional residency had taught them how to cooperate with nurses and doctors without growing resistant or emotional.

The research program, as finally planned and carried out, was composed of two separate sets of experiments. The first, a long-range clinical survey, consisted of giving each day to the 59 children in the rest home a supplementary glass of milk one hour before noon dinner and again one hour before supper. This feeding program was continued for nearly five months. Pasteurized milk and homogenized milk were alternately fed, with observation of the children for symptoms attributable to the added milk before meals.*

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*Pasteurization is an integral part of the homogenizing process. Unless heat treatment accompanies the homogenizing to the extent necessary for killing of pathogenic bacteria, the lipase present will become activated, and the milk grow rancid within a matter of minutes. In this paper the term "pasteurized" refers to plain or unhomogenized pasteurized milk; the term "homogenized" refers to milk which has been both pasteurized and homogenized.

The second part of the program consisted of a shorter but much more detailed dietary balance study. For successive single weeks the spontaneous food intakes of 18 children were measured carefully, in a quantitative comparison of the amounts of food taken: (a) when glasses of pasteurized or (b) homogenized milk were given before each of the three meals, with (c) when the milk before meals was omitted.

Testing two types of milk in this feeding study made it feasible to explore a related but subsidiary problem. From the standpoint of hampering the appetite or food intake, does a hard-curd milk such as pasteurized milk have effects different from those of a soft-curd milk such as homogenized milk? If curd size and texture are the factors responsible, homogenized milk with its smaller softer curds should produce less impairment of appetite than does pasteurized milk. Homogenized milk is the soft-curd milk most widely sold. Pasteurized milk was responsible for the criticisms quoted in the first paragraph of this paper.

In institutions for treatment of children with rheumatic fever it is a common observation that these patients are subject to occasional episodes of nausea and vomiting which come on spontaneously without obvious cause. Though most frequent in the morning, before breakfast, they may occur at any hour of the day or night. For the purposes of the present question this propensity to gastrointestinal irritability was not unwelcome. It might help to evoke or accentuate whatever disturbances are elicitable by milk.

In the first experiment, which was essentially a screening test, it was hoped that by feeding milk before meals to a large number of children over an appreciable length of time a small group of more sensitive children would be discovered who would manifest the expected symptoms of anorexia or gastrointestinal distress more or less regularly. From observation of such children it would be possible to determine whether there were any differences in their reactions to the two forms of milk.

For this experiment all the children in the rest home were used. There were 59 altogether, ranging in age from 3 to 14 years; 28 boys and 31 girls. All were white. Since the girls were housed on the first floor and the boys on the second, each floor having its own serving kitchen, it was expedient to treat the boys as one experimental subgroup, and the girls as the other. Supplements of milk were served to each child twice daily. One 7 ounce glass was given at 11:00 A.M., an hour before dinner, and a second glass at 5:00 P.M., an hour before supper. While homogenized milk was being served on one floor, pasteurized milk was being served on the other. Regularly each month the two types of milk were alternated to avoid the possible influence of a sex difference. These supplementary glasses of milk were given between February 15 and June 30, a continuous period of 19 weeks.

Because the milk, market grade, was purchased in turn from five different Philadelphia dairies, the source each month was a different region of the local milk shed. The changing from one dairy to another was placed midway between the changing of the children from pasteurized to homogenized milk and vice versa. At all times the pasteurized and the homogenized milk came from the

same receiving vats, so that all differences existent between the two were secondary only to the process of homogenizing. In cream content the range was from 3.8 to 4.2 per cent, with a mean approximating 4 per cent. Over the months the curd tension of the pasteurized milk fluctuated between 24 and 43 Gm., with a mean of 33.6 Gm. The homogenized milk had a much lower range—5 to 17 Gm., with a mean of 10.7 Gm.

The children drank the extra milk without urging or coaxing and seemed to enjoy it. Refusals were extremely infrequent. At times a child would request and be given two glasses instead of the customary single serving. Multiplying the number of these feedings of milk before meals by the number of children, yields the round figure of 16,000—representing the approximate number of times that opportunity was afforded for the hypothesized deleterious effect of milk to manifest itself.

No diminution in appetite became evident for any of the 59 children over the period of the study as compared with the weeks immediately preceding or following, neither with the pasteurized nor with the homogenized milk. The requests for second portions were as abundant as ever and coaxing to eat did not become necessary. In fact, during the nineteen weeks the experiment lasted, none of the children were afflicted with an episode of intra-abdominal distress with vomiting, pain, or diarrhea.

In short, on crude observation, no unwelcome symptoms were displayed by any member of this large group of institutionalized children which could be attributed wholly or in part to receiving a glass of milk an hour ahead of a principal meal.

The more quantitative study was accordingly instituted, to ascertain by direct measurement whether taking of milk before meals would cut down the total daily intake of other foods. Accurate records were kept of the amounts and composition of all articles of food taken by each of 18 children given an unlimited diet: (a) during a week when a glass of pasteurized milk was taken three times daily, one hour before each meal; (b) during a week when homogenized milk replaced the pasteurized milk; and (c) during a one-week control period.

The 18 children, white, aged 5 through 11 years, were distributed in three groups, A, B, and C, each composed of three boys and three girls. The average age of the members of group A was 7.3 years; of group B, 7.8 years; of group C, 7.5 years. As judged by Faber's[3] standards for weight as related to height and age, five of the children were overweight, eleven were in normal range, and two were underweight.

The feeding of milk before meals to these groups was staggered, in order to equalize the influence of climatic and other environmental conditions upon appetite and energy requirements:

Group:	A	B	C
1st week	Pasteurized Milk	Homogenized Milk	None
2nd week	Homogenized Milk	None	Pasteurized Milk
3rd week	None	Pasteurized Milk	Homogenized Milk

Save for the added milk, the diets given the three groups were identical in day-to-day composition, and all items were offered in unlimited quantities.

The daily menus were planned independently of this experiment. Their pattern was in accord with common practices of child feeding as determined by the foods available locally. A typical schedule consisted of: Breakfast: dry cereal with milk and sugar, bread and butter, milk; Dinner: meat, a white vegetable, two green vegetables, bread and butter, dessert, milk; Supper: cereal or sandwiches, milk, fresh or stewed fruit. Such a diet meets the nutritional needs of growing children fairly well; its most serious defect was the relatively low content of fresh citrus fruits. Since menus of this type had been in constant use in the institution for a long time, corrective changes were not initiated prior to the feeding experiment in order not to confuse the kitchen personnel. It was thought furthermore that any beneficial effects contributed by the added milk might be demonstrated more prominently if the basic diet were not ideal.

Individual over-large portions of everything were served to the children. As the loaded food trays were prepared in the kitchen the quantities of every item on each plate were weighed or measured accurately; when they were returned to the kitchen similar measurements were taken of the quantities left uneaten. With each meal separate pitchers of pasteurized milk were set out from which each child helped himself to as many glasses as he wanted. The differences between what was served and what was returned gave the amounts ingested. It was not feasible to measure the fluid balances of the children inasmuch as their drinking water was obtained from fountains of the jet type. Glasses of water were not placed on the mealtime trays.

The consumption of nutrients of each child for each week was then computed according to the analytic values compiled by Taylor.[4] Protein, fat, carbohydrate, calcium, phosphorus, iron, vitamin A, thiamine, ascorbic acid, riboflavin, acid-base ratio, and total calories were measured. Totals were prepared to describe the complete intake of all nutrients (a) inclusive of, and (b) exclusive of, the 21 ounces of milk before meals.

Review of the data impressed one with the wide divergences in weekly intakes of the many factors measured. These differences in the amounts taken by the various children bore no obvious correlations with sex or age. Such differences were not unexpected, since, as Macy[5] and others have emphasized, it is common for normal children to exhibiti short-term wide fluctuations in external metabolic equilibriums. In general, however, more of every nutrient was taken in the two weeks when the milk supplements were given than in the control week which was supplement-free. As an example, the findings for weekly caloric intakes are presented (Fig. 1). The increases ranged from 1 to 52 per cent over the controls, except with one boy of 8 years in the week he received pasteurized milk.

The individual children showed marked differences in calories consumed in the respective weeks supplemented with the two forms of milk. Yet, as demonstrated by the almost perfect identity of the mean values for calories, these dissimilarities were without specific regularity. Taking the control week as the 100 per cent base line, there was an 18.8 per cent rise for the week with pas-

teurized milk supplement and a 19.6 per cent rise for the week with homogenized milk supplement.

With biologic data exhibiting marked fluctuations, conclusions are not of significance unless drawn from central tendencies exhibited by the group as a whole. Therefore, for each nutrient, the intake of each child in each separate week was converted to percentages with the control week as 100 per cent, and the mean percentages for the respective experimental weeks computed from these individual percentages. The reason for converting to a percentage basis before proceeding with the calculations rested upon the necessity for each child's intake to have equal weight in the final scoring. Otherwise the greater quantities consumed by some children would overshadow unfairly the smaller amounts taken by others. For ready presentation the final comparisons have been arranged in diagrammatic form (Fig. 2).

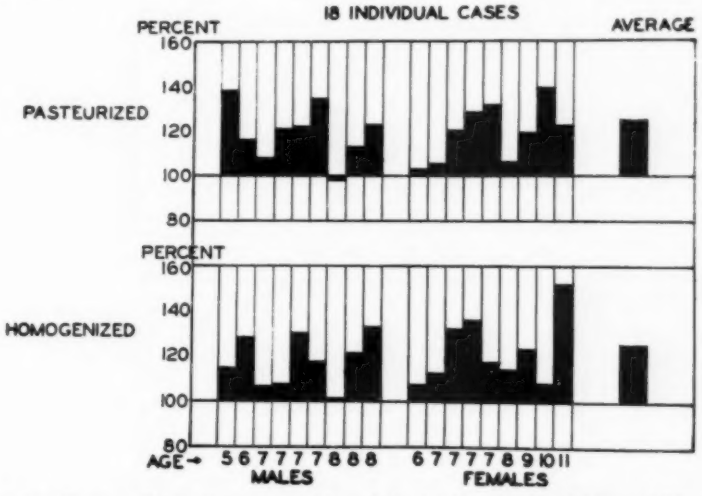

Fig. 1.—Diagram illustrating the weekly caloric intakes of the eighteen children when receiving 21 ounces of supplemental milk per day, 7 ounces before each meal. The base line of 100 per cent is the intake during the control week when extra milk was not given. The upper half of the diagram represents the week with pasteurized milk. Each vertical block represents one child. With one exception all subjects consumed more calories when taking the supplementary milk than in the control week.

By statistical methods, using the t test of significance, the mean values for the weeks with the pasteurized and with the homogenized milk were found not to differ significantly one from another, except with respect to vitamin A. In other words, save for this one vitamin which was augmented only in the week with pasteurized milk, all intake differences between these two weeks were so small as to lie well within the limits of random sampling. The intakes of thiamine, ascorbic acid, riboflavin, calories, protein, fat, calcium, and phosphorus were found to have been augmented markedly in the weeks when milk before meals were given, as compared with the control week which lacked the milk supplements. For only one nutrient, iron, were the intakes during the weeks with milk not increased above the control week.

Fig. 2 demonstrates another point. By deducting from the total intakes during the weeks when one or the other milk was being given the amounts of each nutrient supplied by the milk before meals, it appears that, apart from vitamin A, the amounts of the various nutrients taken *during* meals in each of the three weeks of testing were all about equal. This held true whether homogenized milk, pasteurized milk, or no milk at all had been taken before meals.

The convalescent hospital where these studies were made is efficiently run, with good care of the patients as its primary responsibility. It was of interest to evaluate the quality of the diet of this institution in terms of the nutritional

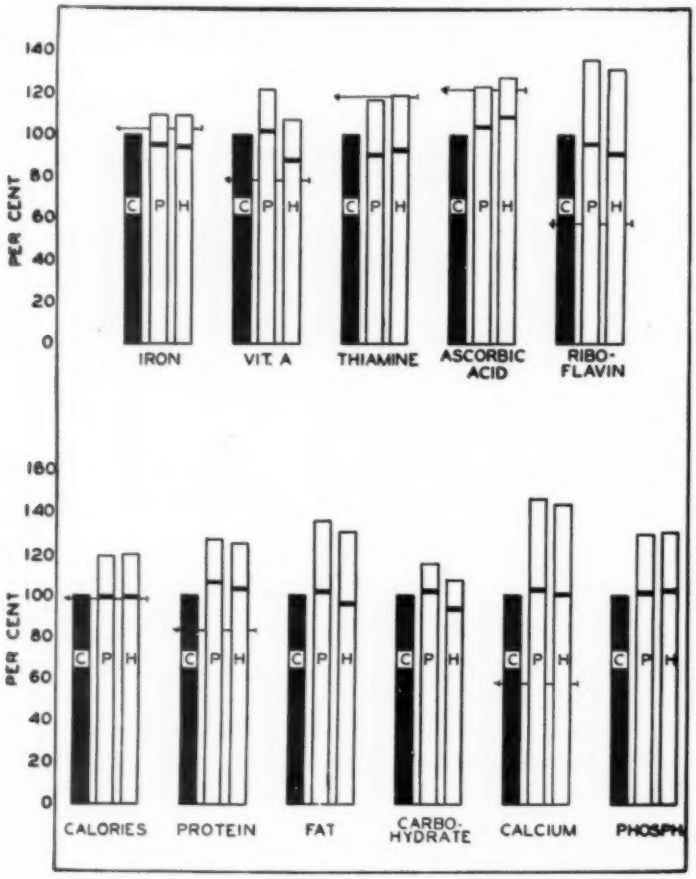

Fig. 2.—Diagram showing the comparative intakes of the nutrients measured. Each vertical block represents the pooled data from 18 children. All figures are relative, the values for the control week being set arbitrarily as 100 per cent. The first (C) unit in each group of three represents the control week with no before-meal milk. The second (P) and third (H) units represent, respectively, the weeks with pasteurized and homogenized milk before meals. The transverse bars in the P and H blocks mark off the fraction of total intake contained in the three glasses of milk (21 ounces) taken as supplements. The arrow symbols on the figures indicate the daily allowances for specific nutrients recommended by the Food and Nutrition Board of the National Research Council.[6]

standards currently proposed by the Committee on Foods and Nutrition of the National Research Council.[6] (Fig. 2) If the amounts furnished by the 21 ounces of milk before meals were disregarded, the institutional diet, as taken to satiety by these eighteen children: (1) supplied protein, calcium, riboflavin, and vitamin A in more than liberal amounts, (2) just met the body needs for iron, (3) was deficient to a moderate degree in thiamine and ascorbic acid, and (4) conformed almost precisely with the proposed standards in caloric energy content. But if the amounts of nutrients in the supplementary 21 ounces of milk before meals were now added to the computations, all shortages became corrected and the consumption of all nutrients including calories became further augmented. Following this study the daily menu of the rest home was altered to include more citrus fruits, cereals, and grains.

The milk before meals did not hamper the appetites of the children for milk during meals. Their daily intakes of milk averaged as follows:

	Before meals	At each meal	Daily total
Control week:		14.9 oz.	44.7 oz.
Week with 3 pasteurized milk pre-feedings:	21 oz.	14.7 oz.	63.2 oz.
Week with 3 homogenized milk pre-feedings:	21 oz.	14.7 oz.	63.2 oz.

These figures mean that every child at each meal helped himself to about two glasses of milk, on the average, regardless of whether or not an extra glass had been taken one hour previously. Of this, approximately 6 ounces daily were taken with the breakfast cereal; the remainder was consumed as a beverage.

If we scrutinize the mean composition of the meals taken during any of the three experimental weeks, we find that the daily 44.2 to 44.7 ounces of milk consumed at those meals supplied (in round numbers) the important percentages of the total intake of nutrients listed in column A:

	A	B
Calcium	85	150
Riboflavin	80	140
Fat	65	
Thiamine	55	45
Phosphorus	50	
Calories	40	40
Protein	35	27.5
Ascorbic Acid	35	
Vitamin A	30	50
Iron	30	27.5
Carbohydrate	30	

Column B lists, for comparison, the proportions of the daily requirements for children, as postulated by the Committee on Foods and Nutrition of the National Research Council, which are met by this volume of milk. Data such as these help to explain why pediatricians have always emphasized the great worth of milk as a food for the child.

COMMENT

Neither of the two sets of experiments furnished any evidence that the taking of milk between meals interferes with the child's eating of his next regular meal. In fact, under the conditions described, milk given before meals proved highly acceptable and seemed to be utilized metabolically by the experimental subjects as a sort of dietary bonus.

These experiments were carried out with a small number of children under specialized conditions, and cannot be taken arbitrarily as the basis for generalizations embracing all children. It is conceivable that different responses to supplementary milk feedings might be observed with children younger, or older, or better nourished, or physically more active, than those in the present series. It is conceivable also that the children here studied, being habituated to institutional living, were more passively receptive to environmental suggestion than children in their own homes would be. They may have viewed the milk before meals as a medicament helpful toward recovery, and therefore to be taken willy-nilly. Life at home and school contains scores of external influences foreign to those of institutional life, and vice versa, all capable of conditioning the child's appetite favorably or otherwise.

It is conceivable, also, that the metabolic needs of convalescent rheumatic fever patients may be greater than nonrheumatic normal children. The average healthy youngster needs daily about 1,600 calories at 4 to 6 years of age, and 2,000 calories at 7 to 9 years of age.[6] A glass of 7 or 8 ounces of milk represents 140 to 160 calories; when served with cookies or bread the caloric content will be 200 or more. If such a feeding is given to a healthy youngster in mid-morning or mid-afternoon, and if in addition his meals earlier that day have been comparatively large, at the next regular meal his appetite may very well be poor, for the reason that a goodly portion of the total daily caloric requirement has been already satisfied. Recovery from a chronic illness such as rheumatic fever may call more urgently for a dietary supplement. Yet it is doubtful that this group of rheumatic fever convalescents were in genuine need of supplemental nourishment. For months prior to the experiments they had been on a liberal diet, with extra food being given between meals. At the time of the test only two were underweight. Moreover, their routine of living was sedentary, with expenditure of energy in physical activities much lower than that of well children being reared at home.

One hypothesis for the recounted unfavorable experiences with milk before meals suggests itself. In extremely cold weather and under other special circumstances market milk sometimes develops a high content of casein and fat and grows markedly hard-curd. Such milk—of curd tension often over 50 Gm.—may give rise to tough rubbery clots inside the stomach. Occasionally a child may suffer from a temporary reflex loss of appetite as a result. In the present study the pasteurized milk had an average curd tension of 33.6 Gm.; the homogenized milk, 10.7 Gm. The pasteurized milk was thus never strongly hard-curd. Perhaps if the digestive capacity of any of the children had been as feeble as that of a young infant, some difficulty might have been experienced in their

digesting of the moderately sized and moderately firm curds from the pasteurized milk. Earlier direct observations[2] of these children, however, had shown every one to have responsive secretory activity normal for the age period. As for homogenized milk, if properly processed and bacteriologically safe, as was the homogenized milk used here, infants can digest it readily without any gastrointestinal distress.[7]

No statements were made by the physicians cited regarding the fat content of the milk presumed to give rise to the digestive disturbances. Guernsey and Jersey milk which contains 5 to 7 per cent fat (and abundant protein in proportion) may be expected to slow gastric emptying more than does milk of commercial grade, such as that in the present study, with fat content ranging between 3.8 and 4.2 per cent.

It must be remembered that the acid of the gastric juice fades out temporarily during fever.[8] The intragastric milk clotting then becomes altered; the coagulation becomes affected by the pepsin enzyme which, when acting alone, tends to produce large calcium-rich curds. Facilitating this trend toward larger curds is the element of fever itself. As the environmental temperature rises above normal body temperature caseinous clots exhibit a marked tendency to shrink by syneresis and grow tough and rubbery. Thus can be explained the nausea and vomiting occasionally seen following the taking of pasteurized milk during febrile illnesses. This tendency, of course, is less marked with homogenized and other more soft-curd milks, which give rise to smaller, softer, and presumably more readily digested curds.

SUMMARY

For nearly five months, 59 convalescent children in a rheumatic fever rest home were given a 7 ounce glass of milk twice daily, one hour before meals, homogenized and pasteurized milk being served in alternate months. These before-meal feedings failed to elicit in any child any undesirable symptoms of anorexia, gastrointestinal distress, or descreased consumption of food attributable to either type of milk.

Eighteen of these children were later subjected to a more quantitative 3-week diet-intake study. Extra milk, pasteurized or homogenized, was given in 7 ounce quantities three times a day, one hour before each meal, for two of the three weeks, and the amounts of food taken spontaneously during mealtimes were carefully measured. It was found that the amounts taken at mealtimes of calories, minerals, protein, and all other nutrients were approximately equal, both in the control week and when milk, whether pasteurized or homogenized, was fed before meals. The added milk proved a true dietary supplement, well taken, and both forms appeared to be equally well metabolized.

No evidence was found in these experiments to warrant advising the discontinuance of drinking milk between meals. The data indicated, on the contrary, that it is wise to make available such extra servings whenever there is need for improving a child's nutritional status or food intake.

Acknowledgment is due Miss Kathleen Cornell for measurement and calculation of the dietary components, and Miss Frances Hoag for many helpful suggestions.

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DYE POISONING IN INFANCY

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RECENTLY two episodes of dye poisoning have occurred on the pediatric service of the Louisville General Hospital, one in the hospital nursery and the other one in the isolation ward.

On Feb. 28, 1945, at 3:00 P.M. it was called to the attention of the pediatric house officers that one of the premature babies had become cyanotic (Case 1). Physical examination failed to reveal a cause for this condition. Four hours later another premature infant (Case 2) in the same unit became cyanotic. The following morning, a third infant (Case 3) was found to have a bluish tint to the lips and skin. Since these were the only babies in this unit, a common etiological agent was suspected. That evening all the newborn babies (thirty-two) in the adjoining nursery showed transient cyanosis. A thorough search for the presence of gas, insecticide sprays, disinfectants, and other poisons was made, but we were unable to discover an agent which could have produced such an episode.

On March 3, one of the nurses stated that on the day the cyanosis appeared, she had helped stamp diapers used in the nursery. It was found that the diapers had been stamped on all corners and both sides before being laundered. The hospital administration had changed their system from a central supply to an individual ward supply, necessitating a stamp for each department. The stamping ink bottle was found and was clearly marked, "This ink contains Aniline Oil which must be removed by laundering before the marked article is stocked or worn."

Case 1.—B. P., premature female, was born Jan. 23, 1945; her birth weight was 3 pounds and ½ ounce. Aside from a positive smear for gonorrhea in the mother, the family and prenatal history was not remarkable. The infant received 0.125 Gm. of oral sulfathiazole prophylactically every eight hours for three days. On February 28, she weighed 4 pounds and 10 ounces, and was receiving 40 c.c. of breast milk every three hours. At 3 P.M. it was discovered by the nurse that the infant was cyanotic. Physical examination failed to disclose the cause. Continuous oxygen was started but in spite of this the condition remained the same. The following day a roentgenogram of the chest (Fig. 1) was made and blood was drawn for methemoglobin determination. The blood had a marked chocolate color and clotted immediately. Blood examination revealed a red blood cell count of 2,540,000 per cubic millimeter with a hemoglobin of 8.5 Gm. per 100 c.c. of blood, and a white blood cell count of 2,650 per cubic millimeter with lymphocytes 47 per cent, polymorphonuclear leukocytes 49 per cent, and monocytes 4 per cent.

On March 2, the infant was still cyanotic. A transfusion of 30 c.c. of citrated blood was given intravenously and penicillin was administered, 2,500 units every three hours intramuscularly. Oxygen was continued due to the persistent cyanosis. On March 5, the red blood cell count was 2,320,000 per cubic millimeter with a hemoglobin of 8.0 Gm. per 100 c.c. of blood, and the white blood cell count was 12,350 per cubic millimeter with lymphocytes

From the Department of Pediatrics, University of Louisville School of Medicine, service of Dr. James W. Bruce and Dr. W. W. Nicholson.

40 per cent, polymorphonuclear leukocytes 50 per cent, and monocytes 10 per cent. The blood Kahn was reported as negative. On March 6, an additional transfusion of 50 c.c. of citrated blood was given intravenously. The cyanosis gradually cleared and the oxygen was discontinued the following day. On March 19, the red blood cell count had gone up to 3,530,000 cells per cubic millimeter and the hemoglobin to 12 Gm. per 100 c.c. of blood.

The infant was discharged April 7, with a weight of 6 pounds and 3 ounces. She has been followed to date, and growth and development are entirely normal.

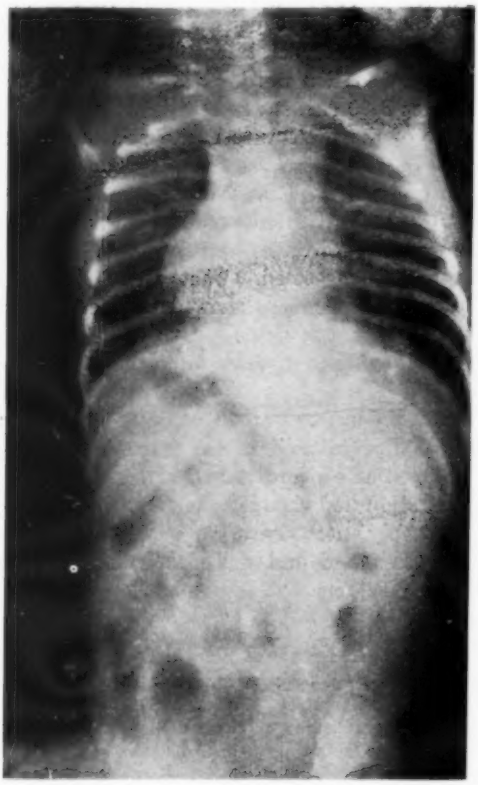

Fig. 1.—B. P. (Case 1). Roentgenogram taken March 1, 1945.

CASE 2.—B. D., premature infant, was born Feb. 17, 1945, after an uncomplicated pregnancy. The birth weight was 2 pounds and 7 ounces. Feedings consisted of a gradual increase of breast milk and water.

On February 28, at 7 P.M., four hours after the appearance of cyanosis in the first child, this infant became cyanotic. Physical examination failed to disclose the cause. The infant was given coramine and oxygen and placed in Trendelenberg position. A roentgenogram of the chest was made the following day (Fig. 2). On March 2, penicillin was started, 2,500 units every three hours intramuscularly, and a transfusion of 30 c.c. citrated blood was given intravenously. Oxygen was continued and on March 3, blood was drawn for methemoglobin determination which was reported as negative; however, there was no evidence of the cyanosis present on this day. On March 5, the infant suddenly expired. Unfortunately no autopsy was obtained.

CASE 3.—B. T., premature infant, was born Feb. 11, 1945, after an uncomplicated pregnancy. The birth weight was 4½ pounds. The mother, who had had antisyphilitic treatment for an infection of long duration, was also a known chronic alcoholic. On March 1, 1945, the infant weighed 5 pounds and 4 ounces and was given 50 c.c. of breast milk every three hours. At 9 A.M., just fourteen hours after the development of cyanosis in the second child, the infant was found to be markedly cyanotic. Twenty c.c. of 2½ per cent glucose in normal saline was given subcutaneously and oxygen was administered. A roentgenogram of the chest was made the following day (Fig. 3). Two thousand and five hundred units of penicillin were given intramuscularly every three hours. A transfusion of 40 c.c. of whole blood was given intravenously. On this date the carbon dioxide combining power was 37.2 volumes per cent.

On March 3, the cyanosis had practically cleared, but as we had just learned the possible etiology, a blood sample was drawn for spectroscopic examination. It was negative for methemoglobin. The following day a red blood cell count was 4,580,000 cells per cubic millimeter with a hemoglobin of 15 Gm. per 100 c.c. of blood, and a white blood cell count of 13,900 per cubic millimeter with lymphocytes 49 per cent, polymorphonuclear leukocytes 41 per cent, and monocytes 10 per cent.

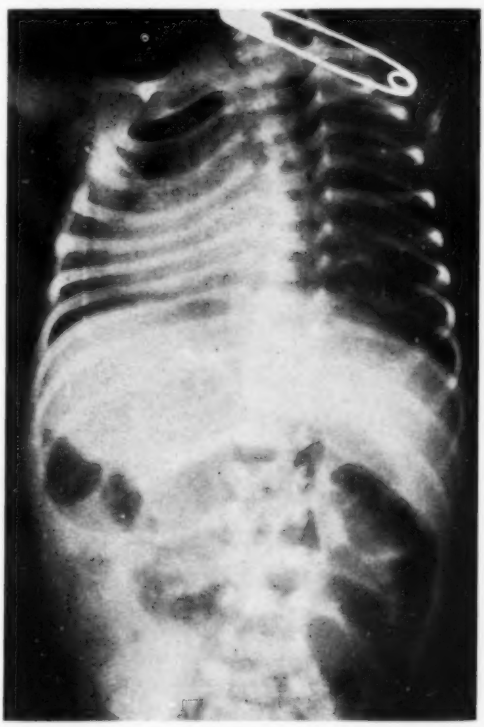

Fig. 2.—B. D. (Case 2). Roentgenogram taken March 1, 1945.

On Sept. 15, 1945, three infants on the isolation ward became cyanotic. These were the smallest of eleven babies admitted to this ward because of nutritional disturbances. All three had severe diarrhea and excoriation of the buttocks. Careful check on all medications failed to reveal any drug which

was being administered to these children which was not also being received by the others. Because of the previous episode, search was made for newly stamped garments. The clothes of these three patients were stamped with aniline dye, but all had been laundered before use. Freshly stamped washcloths were found at the bedsides. The small cloths were stamped eight times and had been used to clean the buttocks of the children. The new linen had been stamped the previous day and placed in a separate compartment so that it could be laundered. That night with a change of nursing personnel these cloths were discovered and used. New towels had also been freshly stamped, but no evidence of their use could be found.

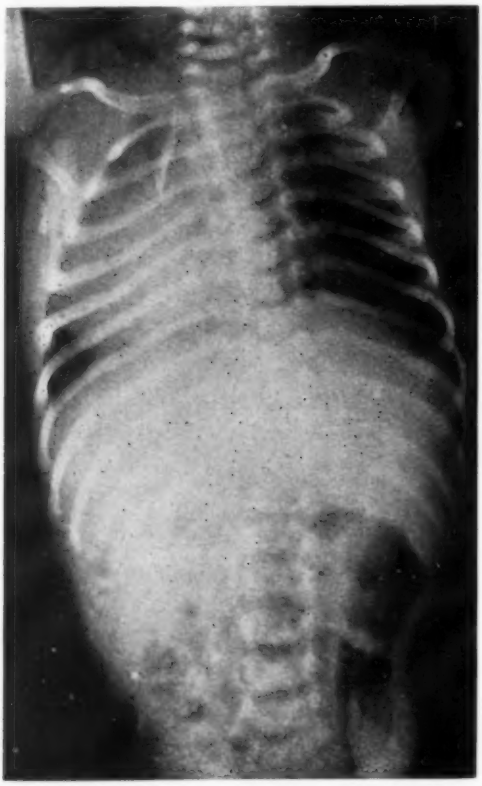

Fig. 3.—B. T. (Case 3). Roentgenogram taken March 2, 1945.

CASE 4.—The first patient, W. J., noted to be cyanotic, was a 3-week-old infant who weighed 5 pounds and 5 ounces. He had been admitted nine days previously because of diarrhea. His weight had increased but he was having four or five watery green stools daily. During the time the freshly stamped washcloths were being used, his buttocks had been washed four times. He also received an oil bath that morning.

At 8 A.M. this child's lips were noticed to be grayish-blue and the skin had a bluish tint. There was no respiratory distress and examination of the heart and lungs was normal.

Eight hours later the cyanosis was very marked and, although no respiratory distress was present, the child was placed in an oxygen tent. There was slight improvement, but four hours later the cyanosis was still severe. At this time 2 mg. of methylene blue in 10 c.c. of normal saline were given intravenously. Recovery was dramatic and within one hour the cyanosis had entirely disappeared. After administration of the methylene blue, the patient was removed from the oxygen tent. The cyanosis did not reappear. There was no reduction found in the red blood cell count or hemoglobin; a blood specimen taken during the cyanotic period revealed methemoglobin.

The child showed no apparent ill effects from the aniline intoxication but the diarrhea continued and the patient died one month later. At autopsy he was found to have small ulcerations of the large bowel, hemorrhagic areas in the pancreas, and an acutely inflamed appendix.

CASE 5.—The second patient, J. M., was an infant 2 months of age who had been admitted to the ward nine days previously because of diarrhea. His weight was 8 pounds and 13 ounces, and he was having about four loose stools a day. This patient was noted to be cyanotic about 9 A.M., but the cyanosis was not marked and disappeared about twelve hours later. No treatment was necessary. No other abnormalities except excoriation of the buttocks were noted. The red blood cell count was 3,440,000 per cubic millimeter, with hemoglobin 11.5 Gm. per 100 c.c. of blood. He gradually improved and suffered no apparent injury from the aniline dye.

CASE 6.—The third patient, W. H., was an infant 3 months old who weighed 7 pounds and 15 ounces. He had been admitted to the isolation ward twenty-two days previously because of severe diarrhea. During the time the freshly stamped washcloths were being used, this patient's buttocks were washed three times. The cyanosis was not discovered until 7 P.M. the night of September 15, which was about eleven hours after the appearance of the first case. Physical examination showed a dehydrated and undernourished white male whose lips, skin, and mucous membranes were cyanotic. No abnormality of the heart or lungs could be found. The buttocks were excoriated. No respiratory difficulty was present. During the night the cyanosis became more marked but gradually disappeared the following afternoon. A transfusion of 75 c.c. of citrated blood had been given on September 15, and the red blood cell count was 3,940,000 per cubic millimeter and hemoglobin 13.5 Gm. per 100 c.c. of blood. Blood taken from the patient during the period of cyanosis was chocolate colored. No treatment was instituted and the cyanosis was present about twenty-four hours.

The patient continued to have diarrhea and expired twenty-one days later. At autopsy the cause of death was found to have been peritonitis involving the spleen and the descending and sigmoid colon.

DISCUSSION

Graubarth and associates[1] reviewed the literature, chemistry, and symptoms of aniline poisoning, and reported seventeen cases which developed in a hospital nursery. In their review of the literature they cited five series of cases, with a total of forty-one patients, of aniline dye poisoning reported by five authors (Raymer, Seligs, Weinberg, Newland, and Ewer). All cases were in infants who had been clothed in freshly stamped linens.

In the first episode herein reported, it is interesting to note all the premature infants were affected, but the full-term babies showed only transient cyanosis. Since the premature infants were affected first, one might think they were more susceptible to the aniline intoxication. However, it may be possible that they were diapered earlier with the aniline stamped linens.

In the second episode the three infants affected had diarrhea with excoriated buttocks. These infants did not wear the freshly stamped linens but

were bathed with the washcloths which were newly stamped by the aniline dye. Wetting and wringing out of these cloths caused the water to turn black.

It is interesting to speculate as to the precipitating factors in the latter group: excoriated buttocks, nutritional disturbance, increased absorption of aniline through the skin due to persistent diarrhea or unknown causes.

Another interesting fact is that three of the affected infants died. In the first group it is possible that the aniline intoxication may have been a factor in the death of one premature infant. In the second group of infants, both deaths occurred at least three weeks later and post-mortem examination revealed the causes of death.

In normal times these two accidents would probably not have happened but, as has been pointed out by others,[1] the hospitals have been confronted with many trying situations such as shortage of diapers, inexperienced help, and frequent turnover of employees. This hospital is no exception.

CONCLUSIONS

1. Two episodes of aniline intoxication are reported. One infant was treated with methylene blue intravenously and recovery was dramatic. Cyanosis, which was most marked in this case, disappeared in one hour as contrasted to the others in this series who remained cyanotic from twelve to twenty-four hours.

2. All hospital linens marked or stamped with an aniline dye should be laundered before use.

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A CASE OF TETRALOGY OF FALLOT WITH ABSENCE OF CEREBELLAR VERMIS; TERMINATION BY BRAIN ABSCESS*

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EIGHTY-SIX authenticated cases of the tetralogy of Fallot had been reported by July, 1941. The full exposition of our case adds to the understanding of the mechanics of this syndrome and records the rare congenital anomaly, absence of the cerebellar vermis.

Peacock[1] first described the tetrad in 1858. In 1888, Fallot designated it as the commonest form of cyanotic congenital heart disease, and it has borne his name since. The tetrad consists of the following four abnormalities: (1) stenosis of the pulmonary valve or stenosis of the pulmonary conus, (2) interventricular septal defect, (3) a dextro-position of the aorta, (4) hypertrophy of the right ventricle.

CASE REPORT

Our patient, a 6-year-old boy, was first seen by us in 1936. Born a blue baby, his condition had long since been diagnosed congenital heart disease without further effort to more sharply define the type.

His appearance was that of a ghastly caricature. An overly large head surmounted a spindly body. A bulbous blue nose stood out on the wizened face. There was a generalized acrocyanosis involving the forearms almost to the elbows and the legs to just below the knees. The color of the nails was purest sky blue untainted by red. The tips of the fingers and toes were moderately clubbed. The boy walked and stood with feet wide apart.

His foster mother, although accepting the diagnosis of congenital heart disease, came to us because she refused to recognize the tiredness and inability to gain weight as part of the picture.

At examination the patient, although cooperative, was slow in his responses. He was often querulous (as if from fatigue). The heart rate was 130 and regular; the sounds were normal except for a second degree, pulmonic systolic murmur. Clinically, the heart was not enlarged; there was no evidence of an endocarditis and none of failure, unless it were in the full veins. The blood pressure was 64/50 in both arms.

The patient was checked every two months as a matter of routine. He was seen through a mild bout of chicken pox and through several respiratory infections. The pulmonic, systolic murmur, while varying from second degree to fifth degree, remained predominantly second degree. On several occasions a superimposed whistle was heard over this same pulmonic area.

In early February, 1938, the patient complained of a dull pain over the upper left precordium on exertion. This pain radiated into the left shoulder. At the onset of the pain, the boy would fall into the nearest chair and remain there until it had vanished. At this juncture a teleoroentgenogram and an electrocardiogram were taken.

The heart shadow was within normal limits. The electrocardiogram (Fig. 1), however, revealed an extreme right axis deviation, a sinus tachycardia of 135, an abnormally high voltage of the QRS complexes, and an exaggerated P_2. $S\text{-}T_2$ was depressed. While compatible with the picture of congenital heart disease and right-sided strain, there was nothing clearly diagnostic of active coronary disease. However, the precordial pain continued to recur with ever-increasing intensity. In mid-March it was complicated by loss of consciousness.

*Title suggested by Maude Abbott in personal communication.
Reported at Clinic of American College of Physicians, Cleveland, Ohio, 1940.

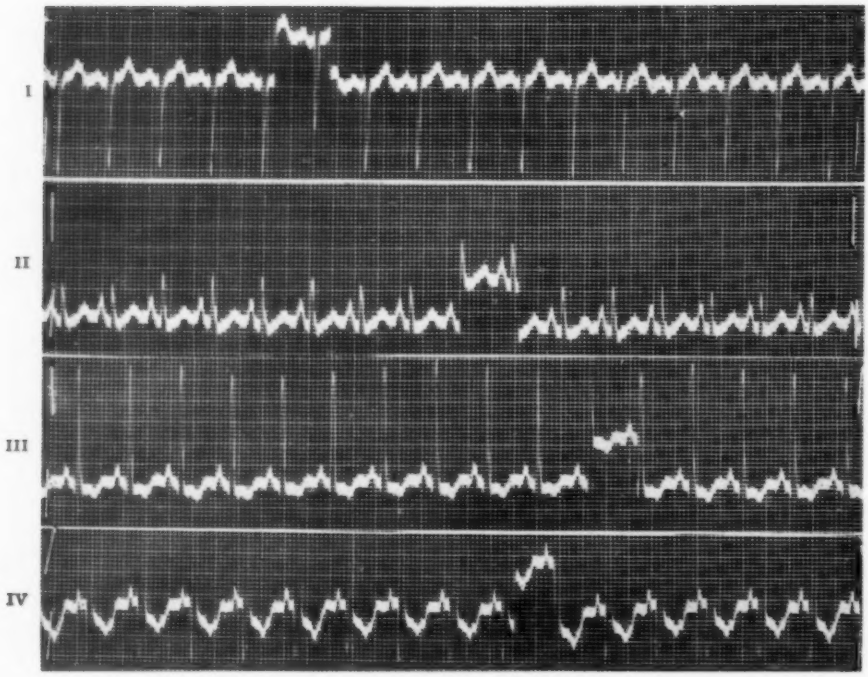

Fig. 1.—Electrocardiogram, February, 1938. Standard limb leads and old Lead IV.

While unconscious, the skin was pale and cold, the heart rate 160 and regular, the pulse thready. The period of unconsciousness varied from one-half to one hour. Though waking free of pain, the patient would recall with fear the initial intense precordial distress. Laboratory findings on March 25, 1938, were 6,500,000 red blood cells and 90 per cent hemoglobin (Sahli). The blood showed a 74.5 per cent oxygen unsaturation. Another sample two weeks later revealed a 66 per cent oxygen unsaturation of the blood.

In May, 1938, oxygen therapy[2] was first employed for the loss of consciousness. Given in full strength through a mask, its effect was a happy one. The patient now regained consciousness in from five to ten minutes and once, when his mother reached him at his first cry of pain, oxygen aborted the pain as well as the expected syncopal attack within two minutes.

Fluoroscopy on Dec. 1, 1938, again showed the heart to be within normal limits and an electrocardiogram taken the same day showed no significant change from the February tracing. Although increasingly short of breath, the patient voiced no new complaints until May 15, 1939, when he complained of a severe headache. The temperature was subnormal and the neurological examination negative. Tending from the first to explain all signs and symptoms on the basis of congenital heart disease alone, we mistakenly ascribed the headache to an increasing hydrocephalus due to an elevated venous pressure. When, therefore, dehydration measures provided temporary relief from the headache, we were more than ever convinced of this assumption. The patient grew listless. His breath was fetid. The gums and cheeks now showed a full-blown gangrenous stomatitis.

On June 2, 1939, a sudden rise of temperature to 103° F., a meningeal cry, a rigid neck, and a spasticity of the right arm and leg first roused us to other possibilities. With the mother invoking death as a blessing, all diagnostic procedures were held in abeyance. The

next day, June 3, 1939, the right arm and leg were completely paralyzed and early papilledema of the left optic disc was noted. The patient expired that evening.

An autopsy performed by Drs. B. S. Kline, Anna M. Young, and one of us (R. W.) revealed numerous congenital abnormalities. In passing, mention is made of three left and two right renal arteries as well as of adhesions between the large and small bowel. The cardiac findings follow: The right auricle was dilated to three to four times the size of the left, and the right ventricle was dilated to the point where it, too, was larger than the left.

The heart weighed 95 grams.	
Tricuspid ring circumference	7.0 cm.
Pulmonary ring circumference	4.5 cm.
Mitral ring circumference	6.0 cm.
Aortic ring circumference	5.0 cm.

These measurements were considered normal for the age. The valve leaflets appeared normal and were fully competent.

Length of right ventricle	6.0 cm.
Length of left ventricle	5.0 cm.
Thickness of right ventricular wall	4-10 mm.
Thickness of left ventricular wall	8-12 mm.

Fig. 2.—Base of brain showing absent olfactory tracts and perforation in the floor of the third ventricle.

There was a defect of the anterior superior interventricular septum measuring 6 cm. in circumference and the aorta, dextroposed to the right, rode over the defect, so that it opened half into the right ventricle and half into the left. While the pulmonary valve was normal, the pulmonary conus beginning just above it and extending upward for 1.5 cm. was constricted to a slitlike channel not over 2.1 cm. in circumference. This channel was further encroached upon by grayish-red vegetations of as much as 3 mm. in diameter. The coronary arteries, dissected to their terminal branches, were patent throughout. Cultures, both of the blood and of the vegetations themselves yielded no growth. Microscopic sections of the myocardium revealed areas of hypertrophy of the cardiac musculature as well as areas of scarring and replacement of the myocardial fibers by relatively acellular fibrous tissue. On the whole, the greatest hypertrophy was subendocardial, whereas the areas of degeneration were subepicardial.

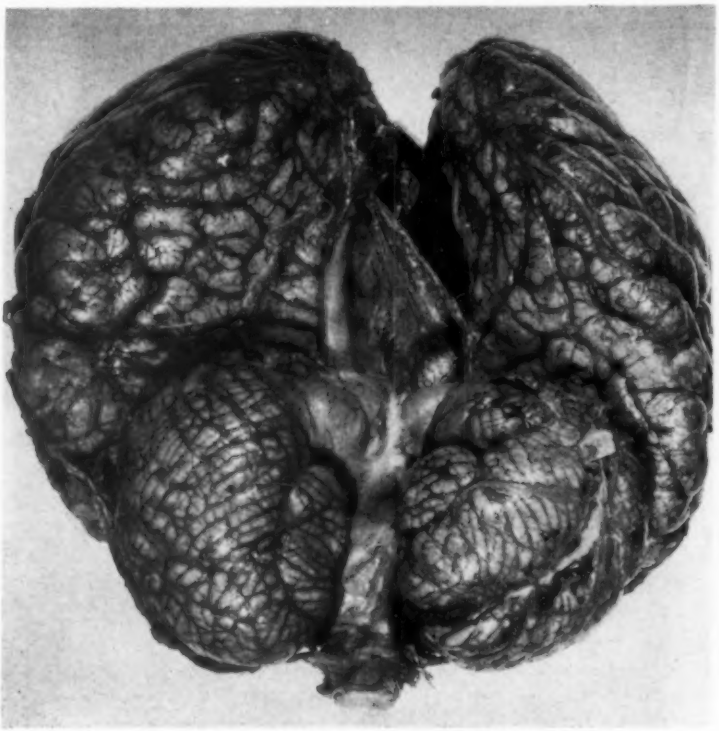

Fig. 3.—Superior view of cerebellum showing absent vermis. The floor of the fourth ventricle is accordingly seen between the lateral hemispheres.

The brain findings follow: The brain was larger than average weighing 1,360 grams. A number of anomalous conditions presented themselves. There were several fenestrations in the falx cerebri. The anterior half of the corpus callosum was absent. Thus, the lateral ventricles presented themselves as indentures from the medial surfaces of the cerebral hemispheres. There was an oval defect in the floor of the third ventricle measuring 1 cm. in greatest diameter (Fig. 2). The cerebellum presented itself as two widely separated lobes due to the absence of the vermis (Fig. 3). The fourth ventricle, accordingly, had no roof and was, in reality, a huge cisterna. The olfactory bulbs and tracts were totally absent (Fig. 2).

The left cerebral hemisphere was considerably larger than the right, and in the left parietal region there was a soft, fluctuant area which was friable and ruptured on slight manipulation. Thick, yellow mucopus was obtained from this opening. Similar purulent material was found in the left lateral and third ventricles. The surface vessels over the cerebral convexities were markedly injected. The venous sinuses were greatly dilated. There was a depression of the calvarium corresponding to the position of the lateral sinuses, measuring 2.5 cm. in diameter. The middle ears, and the sphenoid and ethmoid sinuses showed no gross abnormalities.

The brain was cut coronally after formalin fixation. In repeated sections, the anterior horn of the right lateral ventricle was found to be absent. Posteriorly, the ventricle was enlarged. A communication between the ventricle and the abscess in the left parietal lobe was demonstrated. Both foramina of Munro were dilated and a large portion of the septum between the third and lateral ventricles was absent. The iter appeared dilated. The pons was considerably smaller than average.

Microscopic examination of blocks of brain removed for study showed the following: There was a portion of abscess cavity with central defect filled with polymorphonuclear leukocytes. The surrounding parenchymatous tissue showed typical degenerative changes. The adjacent arachnoid was distended apparently by edema and was richly infiltrated by wandering cells and small leukocytes. In other sections, the architecture of the cerebral cortex and the cellular morphology showed no deviation from the normal. All other structures appeared normal.

COMMENT

A. *The Heart.*—From the first we had difficulty in reconciling our meager clinical findings with the accepted picture of the tetralogy of Fallot. Textbook summarizations of the tetralogy usually agree on a loud, prolonged, systolic murmur heard over the entire precordium, a palpable systolic thrill, marked clinical and x-ray enlargement of the heart, and an overwhelming hypertrophy of the right ventricle. Careful perusal of the literature, however, reveals that many of the cases varied widely from this textbook picture. In 15 per cent of the reported cases the authors failed to note even a systolic murmur while a much larger group noted only a faint murmur. Theoretically, all cyanotic congenital heart diseases (with the exception of the rare cor triloculare), based as they are on a fundamental obstruction to pulmonary flow, should present a marked pulmonic systolic murmur. Our problem is concerned, therefore, with explaining the failure of our case and others in the literature, to meet the excepted picture of the tetrad.

Such an explanation is offered in the graphic diagrams (Figs. 4 and 5) which depict the two extremes of anatomic variation in the tetrad.

While the final word on the causation of murmurs has yet to be said, Lewis, Best and Taylor, and White are fully agreed that the rate of flow is a predominant factor therein. Quoting White[3]: "If the flow is fast, the murmur will be louder; if the flow is slow, the murmur may become fainter, and if the flow is very slow, the murmur may disappear altogether:"

We have observed this same phenomenon in a patient with a button-hole mitral stenosis. The fixation of the valve leaflets, one to the other, verified at autopsy, precluded any widening of the mitral orifice due to dilatation of the ring. Yet, during three acute illnesses, we observed the harsh apical diastolic murmur and thrill vanish, only to recur with the subsidence of the disease as the heart thrust grew in power and the rate of blood flow increased.

Bearing this in mind, the significance of the arrowheads indicating the rate of flow takes on new meaning in Figs. 4 and 5. In Fig. 5 we see illustrated the textbook version of the tetralogy with only a small septal defect. By far the greatest rate of flow (we have chosen an arbitrary three-quarters for purposes of illustration) is through the narrowed pulmonary orifice or conus, resulting in a marked systolic murmur and even thrill. Under the continued strain of expelling blood through a narrowed orifice, the right ventricle has hypertrophied markedly. Contrarily, the cyanosis (as noted in 40 per cent of Abbott's[4] series is not marked since only one-quarter of the right ventricular flow is being shunted to the left.

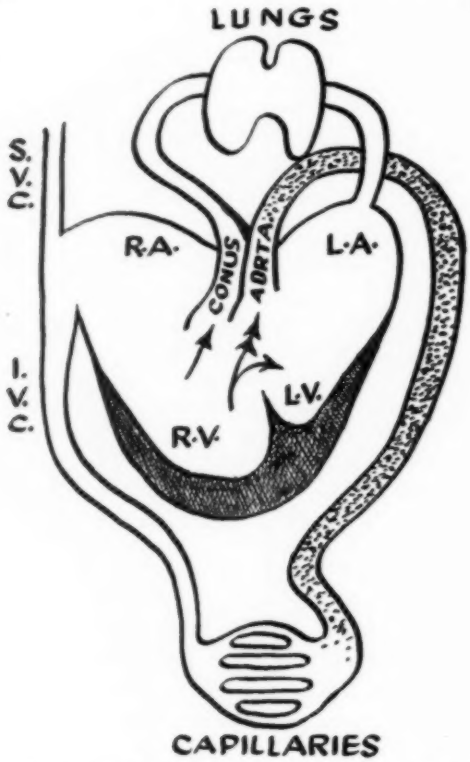

Fig. 4.—Large septal defect. Marked cyanosis. Faint to moderate systolic murmur. X-ray evidence of enlargement not requisite. Note moderate hypertrophy of wall of right ventricle. Number of heads on arrows denotes proportionate rate of flow from right ventricle.

By comparison, the very wide septal defect (in our case seven times as large as the stenotic pulmonary conus) (Fig. 4) results as the arrowheads show, in a diversion of three-quarters of the right ventricular blood flow either into the left ventricle or directly into the aorta. Hence, the remaining one-quarter of the flow through the pulmonary orifice, falling under the "slow" or "very slow" rate of flow referred to by White, is incapable of producing more than

a faint systolic murmur. Further, while this very shunt of three-quarters of the right ventricular blood flow to the left is producing an extreme cyanosis, it is at the same time relieving the right ventricle of much of its pulmonic back pressure. Viewed in this light, a moderate hypertrophy of the right ventricle is all that is to be expected. Heretofore, the cyanosis out of proportion to the right ventricular hypertrophy has been explained away on the basis of a decreased rate of capillary flow resulting from low arterial pressure (Wiggers[5]). With our conception, it is no longer necessary to rely solely on such an explanation of the seeming paradox of extreme cyanosis and only moderate right ventricular hypertrophy.

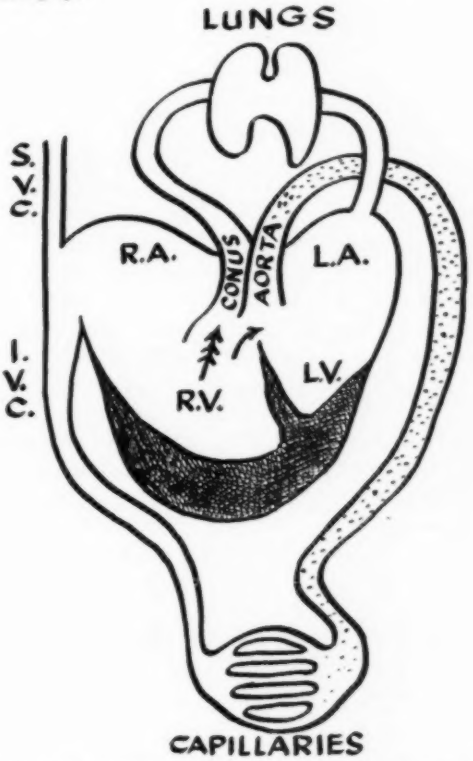

Fig. 5.—Small septal defect. Less extensive cyanosis. Systolic pulmonic murmur and thrill. X-ray enlargement of right ventricle. Note extreme hypertrophy of wall of right ventricle. Number of heads on arrows denotes proportionate rate of flow from right ventricle.

When the autopsy failed to reveal any evidence of coronary disease, we were faced with the task of explaining away both the angina and the minute areas of myocardial degeneration hitherto associated only with capillary thrombosis.

Though it is far from our purpose to enter into a discussion of the various theories regarding angina and myocardial infarction, we cannot refrain from

noting that our case lends support to the dominant role of anoxemia in the production of both.

Thus, while some would insist that cardiac pain is initiated by an accumulation of metabolic (waste) products irritating the afferent nerve fibers of the myocardium, Katz[6] has emphasized the converse of this statement. Since oxygen is a prime requisite for the conversion of these irritative metabolites into non-irritative substances, he points out that no such accumulation is possible in the presence of an unlimited supply of tissue oxygen. Conversely, the irritative substances accumulate wherever there is tissue anoxia, because the oxygen lack halts or slows the conversion of these metabolites.

Smith and Gault[7] in a similar vein, have pointedly referred to the role of anoxemia in myocardial infarction. In those instances in which coronary occlusion did not lead to immediate death, they state: "It results in a localized anemia of the heart muscle and is accompanied by all the degenerative changes associated with anoxemia."

Our patient with his normal coronary flow, with his normal blood count, and, to the best of our knowledge, with other constituents of the blood normal, constituted an excellent situation for the study of the effects of severe anoxia alone upon the heart. The degree of cardiac anoxemia could be determined from the microscopic sections. These showed focal degeneration of cardiac muscle subepicardially and muscular hypertrophy subendocardially. Hence the assumption might be drawn that the subendocardial layer had an accessory oxygen supply. The anatomic presence of the thebesian vessels which traverse the innermost muscle layers offers the only convenient means for an added oxygen transport to the subendocardial layer. That the little oxygen derived from the admittedly small thebesian flow should be the deciding factor between a hypertrophying subendocardial layer and a degenerating subepicardial layer but emphasizes the critical oxygen lack of the cardiac muscle.

In this case, where there were no technical means for measuring the oxygen values of cardiac muscle, these anatomic data serve as the only available index of the extent of oxygen lack. This cardiac anoxia must have been the maximal amount compatible with heart function. The study of this case has given us a physiologic basis for the presence of both angina and tissue degeneration in the absence of coronary obstruction.

The effectiveness of the oxygen therapy is no longer surprising in view of its critical need.

B. *The Brain.*—The most striking of all the anatomic variations in this brain was an aplasia of the cerebellar vermis. Clinically, however, all that was noticed in the patient was a wide-based gait and stance and a tendency to posture the head backward. This picture falls far short of the flocculonodular syndrome described by Botterell and Fulton[8] after experimental lesions in primates. Yet, the persistent, wide-based gait does identify it with this syndrome. Neural compensatory mechanisms were undoubtedly called into play as the child learned to sit up, balance, and finally walk. Accordingly, the neurological picture of this defect became obscured. The reduction in the size of the pons is in proportion to the absence of cerebellar substance.

.Absence of the cerebellar vermis is a rare anomaly. Only two cases, both described by Solovtzoff,[9] were mentioned in a recent review[10] of cerebellar agenesis. Baker[11] described one case in which the cerebellum was totally absent and another in which one of the cerebellar lobes was absent.

In analyzing the absence of the olfactory bulbs and tracts, we are confronted with yet another paradox. The child's mother insisted that he frequently would ask to go into the garden, so that he might smell the flowers. Nevertheless, in the face of anatomic proof, the conclusion must be drawn that the child's mother was either mistaken in her statement or misunderstood his mimicking of other persons' reaction to flowers as the act of smelling.

In the presence of so many anomalous conditions in the brain, it is not surprising to find an associated hydrocephalus. There were at least four situations where ventricular fluid communicated directly with the subarachnoid space. Derangement of flow of cerebrospinal fluid could, of itself, so alter the hydrodynamics within the skull, that a hydrocephalus would result. However, there is another factor which must be considered in the pathogenesis of the hydrocephalus. The chronic elevation of venous pressure as manifested by the great and persistent dilations of neck veins, during life, and the enlarged venous sinuses within the cranium at autopsy, may have been the basis for an increase in cerebrospinal fluid pressure. The presence of increased intracranial pressure before closure of the fontanels, can produce an enlarged skull. In all probability, the hydrocephalic head was due to a combination of these factors. It is to be noted that an Arnold-Chiari deformity was not present in this case.

The origin of the brain abscess which proved to be the proximate cause of death, was undoubtedly embolic. Abscess by contiguity was practically ruled out by the findings in the autopsy that all the cranial air sinuses were uninfected. The vegetations on the heart valves were naturally to be considered as a source of the embolus. However, all indications pointed away from this possibility. First, the vegetations were in the pulmonary stream and thus would be filtered out in the lungs. Second, the vegetations appeared to be in the process of healing and were described as chronic verruca. The chance of emboli being released from the vegetations was, therefore, minimal. The absence of pulmonary embolization would tend to substantiate this contention. Third, *Streptococcus viridans* was not recovered in the culture of the brain abscess or the cardiac vegetations. The absence of the usual organism associated with subacute bacterial endocarditis is significant. Lastly, it is very unlikely that the three pyogens, *Staphylococcus aureus, Bacillus pyocyaneus,* and *Bacillus coli,* actually cultured from the abscess, would all be present in the vegetations on heart valves.

We must, therefore, look elsewhere for a source of the infected embolus containing these three common organisms. The clinical record gives the clue. The patient had a severe mouth infection, with gingivitis. During the course of severe gingival infections, emboli are known to pass from thrombophlebitic veins to the pulmonary circulation (Kline and Berger[12]) and are sometimes the source of lung abscess. These oral infections are due to mixed invaders.

The cardiac anomaly affords the anlage for the venous embolus avoiding the pulmonary circulation and passing directly into the systemic circulation. In this case, in which probably three-quarters of the blood from the great veins was shunted through the interventricular septal defect to the systemic circulation, an infected embolus from the oral region could easily find its way to the brain creating an abscess. It is therefore felt that the brain abscess resulted from paradoxical embolization, the source of which was a badly infected mouth.

This case with its combination of rare cardiac and cerebral anomalies has been a challenge to our conceptions of bodily function. Adequate workup of other such anomalies as may be seen from time to time may well further our knowledge of physiology.

SUMMARY

1. A case is presented of multiple congenital anomalies, the outstanding ones being a tetrad of Fallot and an aplasia of the cerebellar vermis. Exitus was by cerebral abscess.

2. The principal clinical features were: a profound acrocyanosis, bouts of angina complicated by syncope, and cardiac signs which were surprisingly minimal. The patient also presented a hydrocephalic head and moderate signs of cerebellar dysfunction.

3. The principal anatomic findings were: the expected tetrad of Fallot, a healing verrucous endocarditis of the pulmonary conus, a cerebral abscess, and multiple anomalies of the brain, the striking feature of which was an absence of the cerebellar vermis.

4. Explanation is offered for the disparity between clinical signs and anatomic findings in the heart. The pathogenesis of the brain abscess was shown to be an instance of paradoxic embolization.

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CONGENITAL HEMANGIOMA OF THE PAROTID GLAND

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TUMORS of the parotid gland have been described and discussed many times in the literature. It has been our observation, however, that only tumors in adults were adequately described and that congenital tumors were usually mentioned only in a casual way.

Hemangioma or hemangioendothelioma of the parotid gland is one of the rarely mentioned congenital tumors. A description of the tumor, with a personal observation by one of us (K. G.) in *L'Hémangiome de la Parotide*, was published in 1939.[1] After that year there is scant literature on these congenital tumors with only occasional and incomplete mention of their clinical course and prognosis, which, as seen in our case, is of utmost importance for the treatment and subsequent life of the patient.

Judging by the scarcity of the literature, the tumor must be of rare occurrence. In the published cases the majority of the tumors occurred in female children and most of these were situated on the right side.[2] The main diagnostic features are the presence of the tumor at birth or its appearance during the first weeks of life; the unilateral occurrence; the enlargement of the tumor on crying; the elastic consistency, the compressibility, and the lobulation felt upon palpation. The skin covering the tumor may be either normal in appearance or show bluish discoloration, may include a hemangioma, a telangiectasis, or an increased venous design. Signs of inflammation and pain or tenderness are absent in uncomplicated cases.

The tumor takes a rather characteristic and uniformly disastrous course. It usually grows slowly in the beginning, but suddenly, even without any apparent outside stimulation, the speed of its growth increases until the death of the patient, within a few weeks or months, due to invasion and compression of the vital organs of the neck. If surgical intervention occurs, the course is changed considerably. If surgery is radical and all parts of the tumor are removed (this may necessitate trauma to or destruction of a portion of the facial nerve) the prognosis for a permanent cure is favorable. In the cases in which the operation has *not* been radical, either because only a diagnostic biopsy has been performed or because of the fear of injury to the facial nerve, the remaining portion of the tumor continues its growth at a much accelerated pace and the death of the patient is usually hastened. The success of a second operation is usually questionable because of the far-reaching invasion of the surrounding tissues and organs, including the vital blood vessels of the neck.

Microscopic findings which have been reported have been uniform in the description of the types of tissue found. Capillary, cavernous, and endotheliomatous types have been described. Under low magnification there is an al-

From The Children's Memorial Hospital and The Otho S. A. Sprague Memorial Institute.

most homogeneous mass of nuclei. Fibrous septa separate the tissue into a lobulated structure. Under higher magnification a new tissue of vascular nature is seen which replaces large portions of the normal parotid gland. Numerous small capillaries are present, many filled with red blood cells. In some areas the capillaries are collapsed and the tissue has a densely cellular appearance. When the tumor invades the parotid tissue there is a more rapid diminution or replacement of the secretory part as compared with the excretory portion. Invasion of the surrounding tissues is by continuity. No mitotic figures are seen.

CASE REPORT

B. C., a 2½-month-old female child, was admitted to The Children's Memorial Hospital on Dec. 12, 1944. The complaint on admission, as given by the mother, was a swelling of the right cheek, which was first noticed at the age of 2 weeks by an aunt of the child. The swelling was so small that it did not cause any concern until the child had reached the age of 6 weeks. There was never any apparent distress occasioned by the swelling, and the child had never shown any signs of illness. Rapid enlargement, redness, or tenderness of the mass had never been present. Birth history, feeding history, and developmental history were normal. The family history was irrelevant. Physical examination revealed a well-nourished, white female child showing no abnormalities other than a sausage-shaped mass the size of a half-dollar located in the right parotid area. This had no apparent connection with the covering skin or underlying bone. The mass could not be transilluminated, was slightly lobulated and elastic to palpation. The skin over the swelling had a slightly blue tinge.

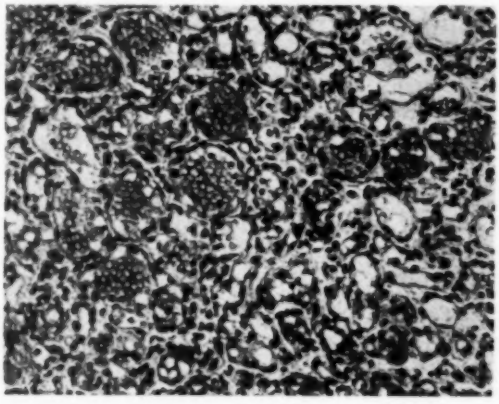

Fig. 1.—Portion of tumor with dilated capillaries.

Because of an upper respiratory infection which developed, the child was discharged and later readmitted to the hospital on Jan. 11, 1945, and operated upon the following day by one of us (L. W. S.). Under ether anesthesia a tumor, 1.5 by 2.5 cm., was removed through an incision paralleling the branches of the facial nerve. The capsule of the tumor was adherent to the surrounding tissues; the base from which it sprang was very deep seated and buried in the parotid gland. A few small branches of the facial nerve were dissected from the tumor and the mass was removed along with a small portion of the parotid tissue. The postoperative course was uneventful.

On March 15, 1945, the child was readmitted to the hospital because of a recurrence of the mass. The following day an operation was performed (two months after the first),

and through the original incision a wide, sharp dissection was employed, with removal of the tumor mass and the adjacent portions of parotid tissue. Several branches of the facial nerve had to be destroyed or stretched rather severely to gain access to the tumor for its removal at this time.

Following the second operation the child received twelve roentgen ray treatments to the right parotid area. The essential factors were filters of ¼ copper and 1 aluminum, using 130 peak kilovolts; 8 milliamperes. The average dose was 170 r at intervals of one week. The postoperative course was uneventful and seven months later there was no evidence of recurrence. There are definite signs of right facial paralysis which were more pronounced immediately after the operation, but still are and most likely will be permanently perceptible.

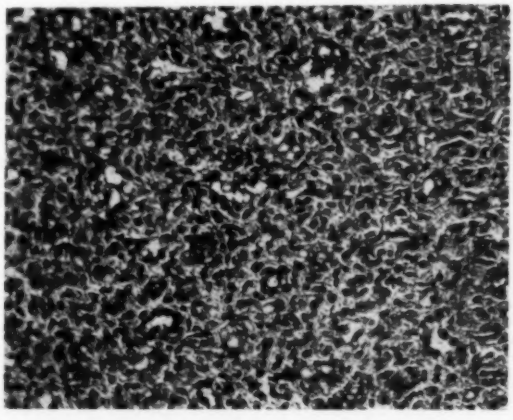

Fig. 2.—Markedly cellular portion of tumor with collapsed capillaries.

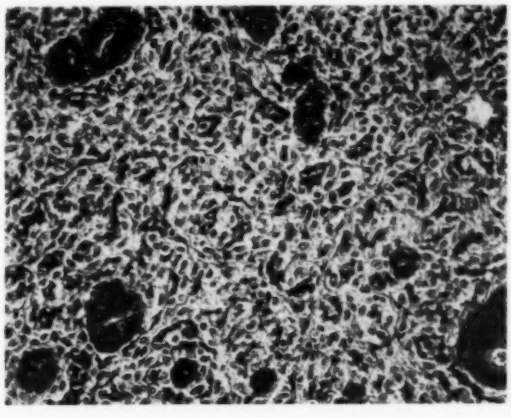

Fig. 3.—Replacement of parotid gland by tumor with only ducts remaining.

The surgical specimens were similar on both occasions. The total mass of tissue received following the second operation weighed 11 grams, the first was not weighed. The tissue was lobulated, semifirm in consistency, and was

surrounded by a rather tough capsule. The color varied from a fatty yellow to a muscle red. No necrosis or cysts were seen grossly. A small nerve was found passing through the largest mass of tissue. Microscopic examination showed salivary tissue in which there was partial or total replacement by vascular tissue. Vascular spaces were numerous (Fig. 1) and many contained red blood cells. In some areas the capillaries were compressed, giving the appearance of densely packed endothelial cells (Fig. 2). The endothelial cells varied considerably in size and shape, had a rather pale cytoplasm, and, except in limited areas where the cells were arranged in fascicles or whorls, assumed no definite polarity. Where there was only partial replacement of the parotid tissue the acinar portion was absent, but ductal tissue was present in moderate amounts (Fig. 3). A few small nerves showed invasion by the tumor tissue. Some areas of the tumor showed good encapsulation. No mitotic figures were seen.

SUMMARY AND CONCLUSION

A case of congenital hemangioendothelioma of the parotid gland is reported. The clinical and pathologic findings as well as the surgical procedures have been described.

The important conclusion to be drawn from the observation of this case and the investigation of the literature is of diagnostic, therapeutic, and prognostic significance. The contrast between the benign appearance of the tumor both macroscopically and microscopically and the highly malignant clinical course is most remarkable. The treatment recommended is the total extirpation of the tumor, sacrificing the facial nerve and parts of the parotid gland if necessary, followed by radiation therapy. If the operation has been early and radical the prognosis is favorable.

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A PRACTICAL URINE OR WET DIAPER SIGNAL

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In 1904, Pflaundler[1] described a device of tinfoil separated by cloth connected to batteries and an electric bell. At first Pflaundler used the device under enuretic children as a wet diaper signal, but soon he discovered that if the device were used continuously under a child for a month or so, the ringing of the bell had therapeutic results. In many cases the knowledge alone that urination in bed would cause a bell to ring seemed to inhibit the act.

In 1908, Genouville[2] and in 1910, Rémy-Roux[3] published papers describing the use of Pflaundler's method which they reported as giving good results. However, the method did not come into general use. Probably the main handicap was that the crude design of the devices made their use very complicated. The Pflaundler pad consisted of two pieces of wire screen separated by a removable piece of linen. A relatively large amount of urine had to pass through the pad to make the bell ring. Rémy-Roux used a layer of absorbent cotton in place of linen.

In 1938, Mowrer[4] improved the Pflaundler apparatus by placing a relay in the pad circuit, thus making it sensitive to smaller amounts of urine; they further improved the pad by permanently quilting the metal screens. These changes made the apparatus function more quickly before the pad became completely wetted, which is desirable.

With this apparatus Mowrer and Mowrer[5] obtained excellent results in a group of thirty children ranging from 3 to 13 years of age. Enuresis was eliminated in all cases. The maximum time required to accomplish this in any child was two months. The promptness of the therapeutic effect depended on the age of the child, his eagerness to overcome his difficulty, and a number of variable factors. One feeble-minded child with an I.Q. of approximately 65 responded satisfactorily.

There have been other similar devices reported in the newspapers and periodicals without descriptions of any therapeutic advantages.

On May 4, 1936, the *Baltimore Sun* printed the following: "Svorllovsh, USSR Russian Science, has just announced to Soviet Motherhood a light which flashes when baby needs changing. Wires from batteries are attached to strips of tinfoil in a special packet beneath the tinfoil. Cloth sandwiched between the tinfoil becomes a conductor when dampened and, presto, the light goes on. The system is already in use in a hospital here."

In 1930, a device which required several pounds of salt to be replaced every time the pad was wetted was given a patent by the patent office.

All of these devices have one common fault. They consist of two conductors separated by an *absorbent nonconductor* which, once it becomes wet, is a conductor and has to replaced or dried, or washed and dried, because of the odor and inoperability of the pad when wet.

The best of these pads is that devised by Mowrer. However, in his instructions it is recommended that several pads be kept on hand and that after each use they be thoroughly dried, preferably in the sun, before being used again.

The device to be described here overcomes all these disadvantages. It is probably even more sensitive than Mowrer's device, because wetting one-half square inch of the pad will cause the bell to ring. Since the pad is made only of rubber and metal, it has no absorbent media and therefore does not have to be dried. Only one pad is necessary for each patient and this pad will last indefinitely. There is practically no objectionable odor from the pads as they are made of rubber and metal with a smooth surface which can be wiped or washed like a rubber sheet. In practice, a diaper is placed over this pad with the bare buttocks resting on the diaper, or the diaper is pinned over the pelvis in the usual manner and the diaper-covered buttocks rest on the pad. In either case, as soon as the wet diaper is lifted off the pad, the bell stops ringing. If there is a pool of urine on the pad simply wiping the top of the pad with a dry end of the diaper makes the pad ready for use again immediately.

The simplicity of its use makes it adaptable as a wet diaper signal when it is desired that the baby's diaper be changed as soon as possible after wetting. While this is routinely desirable it may be especially so when the infant has a diaper rash due to an irritating urine, or if the infant is suffering from any other skin abnormality which contact with urine would aggravate.

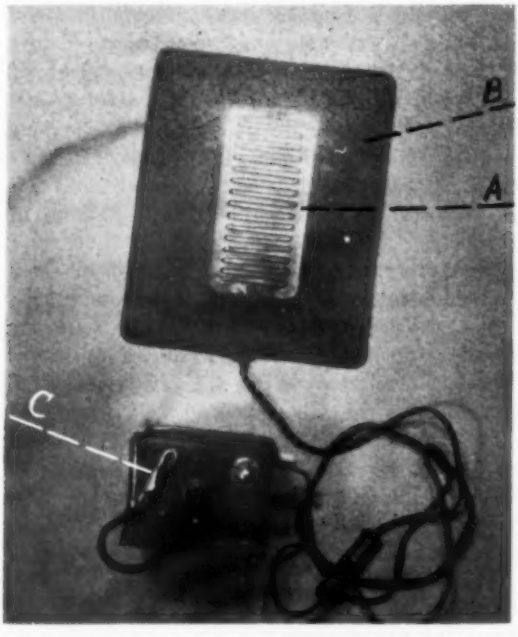

Fig. 1.—*A*, metal grid; *B*, rubber pad; *C*, box containing batteries, relay bell, and switch.

Many other possibilities suggest themselves. It may be used under the buttocks of the incontinent in the presence or absence of decubital ulcers. After a cystostomy it will signal when the tube is blocked off and there is a leakage around the tube in the cystostomy wound.

Since all body fluids contain sufficient electrolyte to operate the device, it may also be used under a patient with a draining gall bladder to signal when there is leakage around the tube in the cholecystostomy wound. Along this line other uses may suggest themselves.

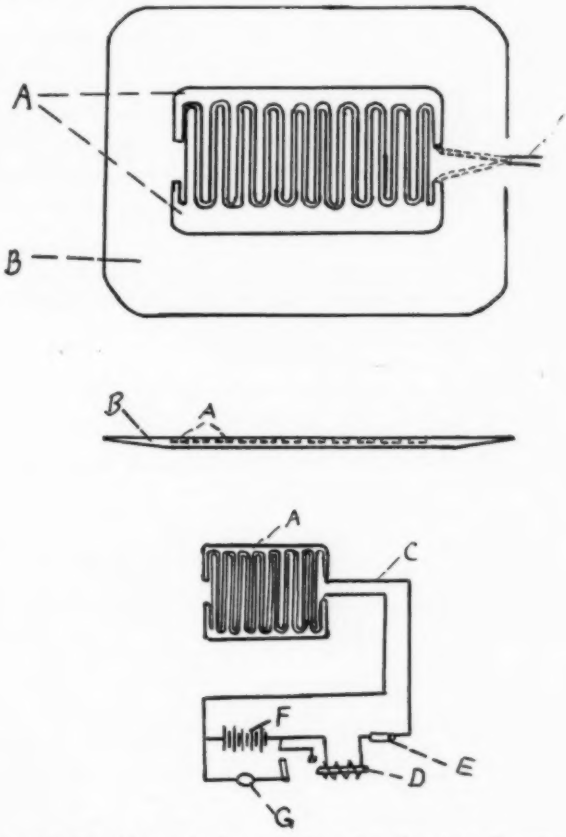

Fig. 2.—*A*, metal grid; *B*, rubber pad; *C*, connecting wire; *D*, relay; *E*, switch; *F*, batteries; *G*, buzzer or other signal.

Fig. 1 is a picture of the device. Fig. 2 outlines its electrical circuit. The device has been made with a light signal instead of a bell in cases where a visual signal would be preferable to an auditory signal, as in a hospital.

The metal grid (*A* in Fig. 1) used in the device has been made of inconel, a noncorroding nickel chrome alloy. This metal grid is 4 inches by 6 inches in size, and .006 inch thick and is cemented to the rubber pad (*B* in Fig. 1). To

adhere the metal grid to the rubber pad a cement called Vulcalox* is satisfactory and after vulcanization in a mold, the metal is flush with the rubber, the pad having an over-all smooth surface. The thickness of the pad is ⅛ inch in the center and it tapers to a thin edge. At the periphery, the edges of the pad measure 12 inches by 18 inches. It is flexible and conforms readily to the contour of the body.

Further manufacturing specifications are: The relay should be a simple relay of 500 ohms. When the pad is used in the treatment of enuresis, a loud bell is provided; but when used as a wet diaper signal in the very small infant or the incontinent, a buzzer is perhaps more agreeable acoustically. The current for the relay and bell is supplied by six flashlight Type D dry cells connected in series. While these cells have to be replaced more often than the larger dry cells, the relatively low cost and ease of replacement make them more desirable. It also makes a compact arrangement, and the customary intermittent use of the device enables these small cells to give many weeks of service before replacement is necessary.

SUMMARY

A device is described, simple in construction and easy to operate, which will signal on contact in the presence of any electrolytic liquid such as urine, bile, or other body fluids.

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*Vulcalox is manufactured by The B. F. Goodrich Company, Akron, Ohio.

Critical Review

ADDISON'S DISEASE IN CHILDREN

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IN RECENT publications, there have been many contradictory statements concerning the number of cases of Addison's disease that have occurred in children under 15 years of age. In addition, the diagnosis of some may be questioned; therefore it was decided that the literature should be scrutinized, in an effort to evaluate each case on its individual merits.

Although Eustachius,[1] in 1563, described the suprarenal glands, it was not until 1849 that Thomas Addison,[2] before the South London Medical Society, made the first announcement concerning the pathologic changes in the adrenal glands. Six years later, in 1855, he published a book, *On the Constitutional and Local Effects of Disease of the Suprarenal Capsules.*[3] He described a train of symptoms that is generally accepted at the present time as indicative of chronic adrenal insufficiency. In this publication, Addison stated: "The leading and characteristic features of the morbid state to which I would direct attention, are anemia, general langor and debility, remarkable feebleness of the heart action, irritability of the stomach, and a peculiar change of colour in the skin, occurring in connection with a diseased condition of the suprarenal capsules."

Of the cases originally described by Addison, six were due to bilateral tuberculosis of the adrenal glands; two cases were caused by metastatic carcinoma involving both adrenal glands; and one was a case of atrophy of the glands. None of these cases occurred in children. Present-day knowledge has very little to add, as far as the symptomatology and etiology are concerned.

In the light of recent discoveries concerning the metabolic disturbances associated with insufficiency of the adrenal glands, it was felt that no reports of patients should be included in the list of proved cases, unless there were evidence either of characteristic blood chemical changes, obvious improvement following adequate therapy over a long period, or autopsy findings demonstrating inadequacy of adrenal cortical tissue.

The symptoms of weakness, anorexia, intestinal upsets, and weight loss are not diagnostic, since any debilitating disease may cause such complaints. Pigmentation of the skin has been described in generalized tuberculosis, chronic nephritis, familial melanoderma, bronze diabetes.

Addison's disease is a clinical and not a pathologic entity. Any process directly or indirectly responsible for destroying the adrenal cortex sufficiently to produce the signs and symptoms described by Addison justifies this diagnosis.

It was not until 1932, that Loeb[4] demonstrated that the sodium level was low and potassium level high in this disease.

It is realized that many of the cases listed under the probable category may have been Addison's disease, but since knowledge of the physiologic and chemical disturbances and potent adrenal extracts was not available at the time many of these were reported, it was impossible to be certain of the diagnoses without autopsy confirmation.

Following is a summary of each case classified as *proved:*

In 1856, Ogle[5] reported a case of a girl, 14 years of age, who had clinical findings of active tuberculosis of the lungs, but, in addition had many symptoms

suggestive of Addison's disease. However, there was no pigmentation of the skin or mucous membranes. Autopsy revealed marked thickening of the adrenal glands with replacement of the natural tissue with tuberculous material. In addition, there was evidence of generalized tuberculosis involving the lungs, left kidney, and bladder. This is the first authentic case of Addison's disease in a child with the pathologic findings substantiating the clinical diagnosis.

In 1857, Fernie[6] described a case of a 14-year-old girl who gradually became debilitated over a period of three years, presenting many of the symptoms and signs of Addison's disease, including peculiar discoloration of the skin. Autopsy revealed active pulmonary tuberculosis of the right lung, and both adrenals were completely replaced by caseous deposits.

In 1858, Hutchinson[7] presented a case of a boy, 11 years old, who became ill with symptoms and signs of Addison's disease and expired a few weeks later following a series of convulsions. The adrenals were found to be completely destroyed by "cheesy material." In addition there was evidence of generalized tuberculous involvement of the mesenteric glands. Up to this time this was the youngest patient of whom a case is recorded. Hutchinson judged it would take at least a year for the adrenals to be filled with masses of "dry, cretaceous deposits." However, the boy had been perfectly well until a few weeks before his death. Ten days before death, he walked a distance of four miles to and from the hospital.

In 1858, Bennett[8] reported the case of a boy, 11 years old, tall, thin, emaciated, and with "bronzed" skin for six months, who had been ill for only a few weeks. He walked to and from the hospital a few days before his death. At post-mortem, both adrenal glands were found to be completely destroyed by tuberculous infiltrations. It appears that Hutchinson and Bennett may have presented the same case.

In 1859, Mackenzie-Bacon[9] described a 15-year-old boy, who had been ill for seven months with anorexia, nausea, weakness, and general pigmentation. Autopsy revealed bilateral tuberculosis of the adrenals and nothing else.

In 1860, Henoch[10] presented a case of a boy, 12 years of age, who had been debilitated for three years. He presented symptoms of marked progressive weakness, chronic cough, periods of vomiting and diarrhea, and he expired following a convulsion which lasted twelve hours. Both adrenals were found to be replaced by calcium and caseous deposits. In addition to the increase in melanin pigment in the skin, there was a generalized bronchial and mesenteric glandular adenopathy with increased pigmentation of these structures. The liver, spleen, and heart were found to be undergoing fatty degeneration.

In 1860, Aldis[11] reported a 12-year-old boy, who had been ill for four months, with olive discoloration of the skin, feeble pulse, vomiting, fainting, and incontinence of the bladder. The diagnosis was confirmed by Addison. Post-mortem revealed that only the adrenals were involved, and they were replaced by a firm, caseous material.

In 1861, Barker[12] described a 14-year-old boy, who for four months had experienced pigmentation of the skin, anorexia, vomiting, pain in the abdomen, and gradual emaciation. At autopsy both suprarenal glands were found to have been completely destroyed by tuberculous deposits. There was also a moderate degree of pulmonary tuberculosis.

In 1861, Broadbent[13] reported a girl, age not given, who had many months of debility, low-grade fever, discoloration of the skin and chorea. At autopsy both adrenal glands showed "scrofulous" deposits, but there were no other significant findings.

In 1861, Montgomery[14] described a case of a boy, 14 years of age, who became ill and expired after a period of five months. He had many of the symp-

toms of Addison's disease. It was found that the adrenals were completely destroyed by tuberculous material and evidence of healing tuberculosis was found in both lungs. The skin showed the usual change in color.

In 1862, Wilks[15] described the case of a boy, 13 years of age, whose condition was diagnosed as this disease by Thomas Addison. This child presented a picture of marked emaciation, incontinence of the bladder, dehydration, marked asthenia, and generalized pigmentation of the skin, of four months' duration. Post-mortem examination revealed no traces of normal adrenal tissue, this being entirely replaced by "tough, yellow amorphous tuberculous material." No evidence of pulmonary tuberculosis was found.

In 1864, Murchison[16] reported a 15-year-old boy, who had anemia and discoloration of the skin for one year. He also had diarrhea, vomiting, and color like a "Negro." Cause of death was erysipelas of the face. Autopsy revealed old pulmonary tuberculosis, tuberculous peritonitis, and large caseous adrenals.

In 1865, Murchison[17] presented a 15-year-old boy, ill more than one year, who had an occasional convulsion, pain in the back, diarrhea, and clinical findings of tuberculous peritonitis, and pigmentation. Autopsy showed tuberculosis of the lungs, peritoneum, and both adrenals.

In 1865, Greenhow[18] described a 13-year-old girl, who had all the classical symptoms and signs of Addison's disease for six months before death. Autopsy revealed generalized tuberculosis involving the mesenteric glands, and lungs, and both adrenal glands were completely destroyed by cheesy material.

In 1866, Rossignol[19] reported a 15-year-old girl with "bronzing" skin, generalized weakness, and anorexia for two months. Both adrenals were enlarged, two inches long, filled with hard, yellow "putty like" material.

In 1866, Parker[20] described a 15-year-old girl, with a seven weeks' illness with asthenia, vomiting, weight loss, and "melanoderma." Post-mortem revealed pulmonary tuberculosis and caseous adrenals.

In 1866, Little[21] presented the case of a 15-year-old girl, who had been delicate "all of her life" but had no definite illness until four weeks before her death. There were symptoms of weakness, vomiting, "fainting attacks," and generalized pigmentation of the skin and mucous membranes. Autopsy findings revealed tuberculosis of the lungs and adrenals.

In 1866, Faure and Barthez[22] described a 14-year-old boy with pigmentation of the skin for one year, intermittent convulsions, weakness, attacks of diarrhea. Autopsy showed "congestion of meninges," supposedly tuberculous meningitis, and tuberculosis of both adrenals.

In 1867, Heckford[23] reported a 14-year-old girl, who had been treated for arthritis in the hospital. Her complexion was "gypsy like," and she had attacks of convulsions, weakness, and somnolence. There was no diagnosis during life. Post-mortem revealed tuberculous degeneration of both adrenals, nothing else.

In 1868, Arnott[24] described a boy, 13 years of age, with extensive tuberculosis of the spine and many other bones. There was slight bronzing of the skin. Post-mortem showed amyloid disease of the spleen and lungs, but the bronchial glands were free of disease. Kidneys and left suprarenal gland were normal. The right adrenal was large, nodular, and contained many caseous deposits. There was some ulceration of the intestines and large mesenteric glands. The lungs were clear.

In 1870, Guttman[25] presented the case of a girl, aged 11 years, who had been debilitated for a year, and whose death was sudden with gastrointestinal symptoms predominating. There was pigmentation of the skin. At autopsy the right adrenal was found intact, and the left adrenal contained a large, calcified focus.

In 1872, Nicholson[26] reported a case of a boy, 14 years old, who had classical signs and symptoms of Addison's disease. Autopsy showed both adrenal glands to be completely destroyed by tuberculous material. There was no evidence of tuberculosis elsewhere.

In 1876, Andrew[27] described a 15-year-old boy, with generalized bronzing of the skin, and discolored mucous membranes. There was weakness, intestinal upsets, crepitation at right lung base, pain in the kidneys, and increasing cough. He had had three attacks of rheumatic fever in the past three years. Postmortem showed the thymus to be enlarged, hemorrhage in the pleural space, and findings of endocarditis. Both adrenals contained a large amount of caseous material.

In 1876, Pye-Smith[28] reported a case of a 14-year-old boy with signs and symptoms of Addison's disease. Three hours before death, he screamed with pain and became unconscious. At autopsy there was calcification of the adrenal glands, and tuberculous involvement of the bronchial glands.

In 1877, Carter[29] described a boy, aged 14 years, with recurrent attacks of severe headache and vomiting. There was no discoloration of the skin; however, autopsy revealed that both adrenals were completely destroyed by tuberculous lesions and, in addition, there was active tuberculosis of both lungs.

In 1879, Renton[30] presented a girl, aged 13 years, who had been debilitated for many months, with gradual weight loss, weakness, and a marked "melanoderma." Necropsy revealed extensive tuberculosis involving numerous abdominal glands, a direct extension of the tuberculous process into the sheath of the solar plexus, and marked degeneration of the adrenal glands and associated sympathetic ganglia.

In 1879, Smith-Shand[31] briefly described a boy, aged 13 years, whom they saw for the first time in a moribund condition. Marked emaciation and generalized pigmentation of the skin and mucous membranes were reported, and both adrenal glands were said to be in an "abnormal state." The exact nature of the pathologic process was not given. The patient's hair looked as if "it had been washed with a solution of nitrate of silver."

In 1881, Wright[32] described a boy who had been ill for three years with symptoms of active pulmonary tuberculosis, but in addition there was definite generalized pigmentation. The patient expired when 8 years of age, and the right adrenal and right kidney were found to be completely destroyed by caseous material. The left adrenal was intact. There was a history of tuberculosis in the family.

In 1882, Franks[33] presented a case of a girl, aged 14 years, who had been ill for two months with typical symptoms of Addison's disease. Both her father and mother were known to have had active pulmonary tuberculosis. At autopsy there was generalized tuberculosis of the mesenteric glands, caseous deposits in both adrenals, and active tuberculosis of the left lung.

In 1883, West[34] described the case of a girl, aged 14 years, who had symptoms for two years consisting of marked weakness, loss of weight, abdominal discomfort, and frequent fainting episodes. There was an increased pigmentation of the skin and mucous membranes, and at necropsy there was tuberculous involvement of both adrenal glands and widespread pulmonary tuberculosis.

In 1883, Church[35] reported a case of a girl, aged 9½ years, who had a history of intimate exposure to active tuberculosis in the family. For twelve months she exhibited classical signs and symptoms of Addison's disease and expired following a convulsion. The left adrenal was replaced by tuberculous material, and on sectioning the right adrenal a large calcareous body was seen. In addition, there was evidence of old tuberculosis involving the left pulmonary apex.

In 1885, Monti[36] described a case of a boy, 10 years of age, who had symptoms over a period of three years suggestive of the diagnosis of chronic adrenal insufficiency. He expired following a period of convulsions and coma. There was marked generalized pigmentation of the skin. The autopsy findings in this case were very unusual in that the right adrenal was completely absent and the left was unusually small and atrophied. There was a mild, generalized hyperplasia of all lymph glands and enlargement of the spleen. The atrophy of the adrenal gland was thought to be due to "chronic interstitial inflammation." There was no evidence of tuberculosis. This is the first case of atrophy of the adrenal reported in a child.

In 1893, Augagneur and Berard[37] presented a case of a girl, aged 12 years, with typical symptoms of Addison's disease with pigmentation of the skin. Grafting of adrenal tissue was attempted but this was followed by hyperpyrexia, vomiting, diarrhea, and death within a few hours. In addition to a diffuse tuberculosis of both adrenal glands, there was evidence of tuberculous peritonitis and active pulmonary tuberculosis.

In 1893, Descroizilles[38] described a girl, aged 14 years, with typical symptoms and signs of Addison's disease, ending with a severe diarrhea and death, one year later. Tuberculous involvement of both adrenal glands was found, and in addition there was some enlargement of all the glands throughout the body, including the thymus.

In 1895, Schotte and Risel,[39] cited by Dezirot, reported a case of a 15-year-old girl, who was ill for approximately a year with anorexia, nausea, and constipation. Autopsy revealed pulmonary tuberculosis, and the adrenal glands were replaced by cartilaginous tuberculous masses.

In 1895, Descroizilles[40] presented a 14½-year-old girl with asthenia, weight loss, fever, cough and vomiting, and pigmentation, of three months' duration. Her mother had pulmonary tuberculosis. Autopsy revealed pulmonary tuberculosis, large thymus weighing 30 grams, enlarged mesenteric glands, and both adrenals caseous.

In 1895, Anglade and Jacquin[41] described a mentally retarded girl 4 years of age, who developed generalized pigmentation of the skin shortly before death. Both adrenal glands were said to be sclerotic and markedly atrophied. There was generalized atrophy of the brain, especially noticeable in the frontal lobes and there were a few tubercles throughout the cervical cord and lungs.

In 1897, Schilling[42] reported a case of a boy, aged 13 years, who presented the classical signs and symptoms of Addison's disease with short periods of remissions and exacerbations, and death three years later. Autopsy revealed tuberculous involvement of both adrenal glands, not associated with active tuberculosis elsewhere.

In 1897, Bury[43] reported a case of a girl, 13 years of age, who had "mulatto" appearance of the skin for two years and for one year had been bothered with generalized weakness and frequent intestinal upsets. A diagnosis of Addison's disease was made. "The suprarenal capsules from sheep were pounded up in a mortar with glycerine and a teaspoonful of this mixture was given three times a day." A few days later she expired. Post-mortem examination was made, and the adrenals were found to be completely destroyed by a tuberculous process. There were no pathologic changes elsewhere.

In 1898, Legg, Wickham, and Ormerod[44] described a 15-year-old boy, presenting typical signs and symptoms. He had weakness, anorexia, weight loss, and pigmentation. Autopsy showed tuberculosis of the right lung, mesenteric glands, and both adrenals.

In 1898, Moizard and Bernheim[45] published a case of an Italian boy, aged 14 years, with typical signs and symptoms of Addison's disease, and death in two months' time. There were findings of generalized miliary tuberculosis in-

volving the lungs, intestines, spleen, liver, and kidneys. Both adrenals were completely destroyed.

In 1899, Lartigau and Happel[46] presented a case of a 12-year-old boy, who was ill five or six weeks, with a "tired feeling" which gradually increased in severity and was associated with marked vertigo and dyspnea on very slight exertion. There were also recurring gastrointestinal symptoms. The child was very small for his age and had an emaciated appearance, subnormal temperature, and a weak, feeble pulse. The skin was "copper discolored." The pigmentation was especially noticeable over the backs of the hands, forehead, temples, nipples, scrotum, and penis. The patient gradually improved for a period, although pigmentation of the skin became increasingly worse. Death was sudden, following a generalized convulsion. Autopsy revealed diffuse tuberculous involvement of the lung, and caseation of both adrenal glands.

In 1900, Netter[47] described the case of a 3-year-old girl, who was apparently healthy until three days before death. She had slight but generalized pigmentation of the skin, vomiting, diarrhea, and signs of peritonitis. Both adrenals were found to be tuberculous.

In 1900, Nattan and Larrier[48] described a case of a boy, aged 13 years, who for seven years had "recurring cold abscesses" and suddenly became ill with extreme exhaustion, vomiting and diarrhea, and bizarre mental reactions which may be interpreted as those associated with hypoglycemia. In addition, there was a generalized pigmentation of the skin. At autopsy both adrenal glands were found to be completely replaced by caseous material.

In 1904, Nobecourt[49] presented a case of a boy, aged 13 years, with classical signs and symptoms of Addison's disease. Death came suddenly, following a generalized convulsion. There was active pulmonary tuberculosis and a tuberculous process involving the mesenteric glands and both adrenals.

In 1905, Anglade and Jacquin[50] described a mentally retarded girl, aged 12 years, who presented a gradual downhill course, characterized by periods of vomiting and diarrhea. There was generalized pigmentation of the skin. At autopsy, evidence of miliary tuberculosis, involving all organs of the body, was found. The normal structure of the adrenal glands was completely replaced by the tuberculous process.

In 1905, Nobecourt and Paisser[51] published a report of a 13-year-old boy who displayed the usual symptoms of Addison's disease with generalized discoloration of the skin. The adrenals and adjacent mesenteric glands were found to be tuberculous.

In 1913, Langmead[52] presented a case of a boy aged 10 years, living with four relatives, all of whom later died of pulmonary tuberculosis. There was mild generalized pigmentation of the skin of a year's duration and only a moderate degree of weakness. The child suddenly became ill with persistent vomiting and loss of consciousness; he expired within a few hours. Post-mortem examination showed generalized tuberculosis involving both adrenal glands, lungs, and liver. The spleen was enlarged and the heart was very small.

In 1917, Klein and Kux[53] described a case of a boy, aged 12 years, with the history of intimate exposure to active tuberculosis in his immediate family. There was a gradual downhill course over a period of a few months, associated with listlessness, mild but generalized pigmentation, and weight loss. Post-mortem revealed generalized tuberculosis, with extensive involvement of both adrenals.

In 1917, Comby[54] presented a case of a girl, aged 13 years, with the usual symptoms of Addison's disease. The skin showed generalized pigmentation. There was a history of tuberculosis in the family. Autopsy revealed generalized tuberculosis involving the lungs. There was extensive destruction of the right adrenal and right kidney. The left adrenal was also involved, but to a lesser extent.

In 1933, Duff and Bernstein[55] described what is probably the first case reported in the American literature, of atrophy of the adrenal gland causing Addison's disease. This boy, aged 14 years, expired at Johns Hopkins Hospital, July 29, 1901. He had had three previous admissions to the hospital, had severe measles at 2 years, whooping cough at 5 years, scarlet fever at 7 years. At 8 years, he had chills and fever, which were diagnosed as malaria, and at that time generalized pigmentation of the skin was noticed. The mother stated that the child had had some increase in pigmentation since the age of 6 years. His condition was diagnosed as Addison's disease at 10 years of age. He had always been active and had no intestinal upsets. On his last admission to the hospital in 1901, he had typhoid fever, to which he succumbed within a few days. Dr. E. L. Opie performed the autopsy and gave the anatomical diagnosis, "Addison's disease, and atrophy of the adrenal cortex with lymphocytic infiltration in the cortex and medulla. The spleen, intestinal tract and mesenteric glands were that of typhoid." There was no evidence of active tuberculosis. The adrenals were very small and together weighed only 2.2 grams.

In 1935, Thompson[56] described a case of a girl, aged 10 years, with typical symptoms and signs of Addison's disease of six months' duration, ending with sudden death following a period of unconsciousness. There was tuberculous involvement of both adrenal glands and all abdominal glands.

In 1935, Snelling and Erb[57] described a case of a boy, 9½ years of age, presenting the usual signs of marked emaciation, asthenia, pigmentation, and low blood pressure, and sudden death following convulsion. The heart was found to be very small, weighing only 77 grams, and there was a marked atrophy of both adrenal glands, leaving only a few cortical cells in the left gland; no semblance of cortex could be found in the right. The right gland weighed only 1.4 grams and the left gland, 1.6 grams. The cause of this atrophy is not known. There was no evidence of tuberculosis.

In 1936, Friedman[58] reported a case of a boy, aged 12 years, presenting a downhill course of six months' duration, with tuberculosis of the lungs, generalized weakness, weight loss, low blood pressure, but with no pigmentation of the skin or mucous membranes. Post-mortem examination, however, revealed a definite tuberculous involvement of both adrenal glands in addition to the pulmonary involvement.

In 1939, Butler, Ross, and Talbot[59] presented a very interesting case of a 20-month-old boy, who had the following signs and symptoms: From the age of 2 weeks, macrogenitosomia, brownish pigmentation of skin, sudden collapse on restriction of fluids, or on removal of added salt in the diet. During periods of collapse the patient would become dehydrated, show lowering of serum sodium and elevation of serum potassium concentrations. Excessive amounts of estrogen and androgen were excreted in the urine. The child was maintained in fairly good nutritional balance by the daily addition of 2 to 3 Gm. of sodium chloride and 1 or 2 Gm. of sodium bicarbonate to the diet. This is the first and youngest reported case of macrogentiosomia associated with typical signs and symptoms of Addison's disease. The patient was alive and doing well, without the use of cortical extracts or desoxycorticosterone. No follow-up has been reported.

In 1939, Renshaw and Manning[60] presented a case of a boy, aged 12 years, with signs and symptoms suggestive of appendicitis. He had recurring abdominal discomfort over a period of two years, and expired shortly after entering the hospital. The right kidney was found to contain a small tubercle, and both adrenal glands showed marked caseation with little calcification. There was a generalized brownish pigmentation of the skin.

In 1940, Wilkins, Fleischmann and Howard[61] described a case of "macrogenitosomia precox, associated with hyperplasia of the androgenic tissue of

the adrenal and death from cortico-adrenal insufficiency." This was a 3½-year-old boy, who presented precocious development of the sex organs since the early months of life. It was interesting to note that a sibling was a female pseudohermaphrodite. The child showed a mild, but diffusely increased pigmentation of the skin and gums. In Addition, there was a low blood sodium, high nonprotein nitrogen, and a decided craving for salt. The patient died suddenly. The adrenal cortex was largely composed of androgenic tissue, apparently replacing all other elements of the cortex. The testes were also enlarged and composed of "androgenic zone" tissue. As the author states, this is the first case with definite proof that death from adrenal insufficiency resulted from the destruction of the cortex of the adrenals by encroachment of the androgenic zone.

In 1940, Ginandes[62] described the case of a 12-year-old boy, with a history of exposure to tuberculosis by his father. He developed progressive asthenia, emaciation, and pigmentation of the skin and mucous membranes. The blood pressure was very low, the basal metabolic rate was –33, and the tuberculin test was positive. X-ray showed a very small "drop-type" heart. There was a dramatic response to administration of glucose and sodium chloride solution intravenously. X-rays of the abdomen showed some calcification of the adrenal glands. Blood chemistry revealed low serum sodium and high potassium. The patient was placed on a diet low in potassium, high in sodium and vitamins, but because of several crises, adrenal cortical extract was given daily. The child took this for one year and showed definite improvement. He gained weight and at the end of this time had a normal blood pressure and normal sodium and potassium levels. The author states that desoxycorticosterone acetate will be tried shortly. No follow-up reports were given.

In 1941, Thelander and Cholffin[63] presented a very interesting case and should be complimented for making an accurate diagnosis of such a young child. The patient was a boy, birth weight 7 pounds, 10 ounces, requiring resuscitation because the cord was wrapped around the neck three times. The child improved and nursed well three days later. At the age of 8 days, a few loose stools were noticed; this was followed by a weight loss and regurgitation of food. At 11 days of age, the baby became sleepy, was difficult to rouse, and the stools remained loose. The child was given salt and water solution by mouth, a blood transfusion and parenteral fluids. At 3 weeks of age, the weight was 6 pounds, 7 ounces, and a diagnosis of probable adrenal insufficiency was made. At 1 month of age, there was sudden collapse and the following day the blood sugar was 74 mg. per cent and blood chloride 441 mg. per cent. The child was given 0.2 c.c. of percortin (desoxycorticosterone acetate) by hypodermic injection, and saline was added to the formula. Immediately following this, the patient began to gain weight and was discharged from the hospital with instructions to the mother to continue the injections of cortical extract. The penis was quite large at birth, but at 6 months of age, the enlargement was unmistakable; pubic hair and a low deep voice were noted. At 9 months of age, the child was readmitted to the hospital with exanthem subitum and has since done quite well on desoxycorticosterone in propylene glycol, 3 drops five to six times a day, sublingually.

In 1942, Anderson[64] wrote a very excellent paper, entitled, *Significance of Adrenal Insufficiency in Childhood*, and reported a case of primary Addison's disease in an 11-year-old boy. This boy manifested all the clinical signs and symptoms characteristic of Addison's disease. The child was well until 10 years of age, when he became listless and an extensive tanning of the skin noted during the summer failed to disappear the following winter. In addition, there was a gradual increase in weakness, frequent episodes of nausea and vomiting,

and a definite craving for salt. Physical examination revealed a deep, generalized pigmentation of the mucous membranes and cheeks. The heart was small, and the testicle was absent on the right. After a fifteen-hour fast, the blood pressure dropped to 62/38, serum chlorides were 355 mg. per cent; sodium, 299 mg. per cent; potassium 28 mg. per cent; and urea nitrogen, 33 mg. per cent. The fasting blood sugar was 89 mg. per cent, and the carbon-dioxide combining power of the blood was 49 volumes per cent. The tuberculin and Wassermann tests were negative. The intravenous pylograms were nonrevealing. Intravenous glucose with sodium chloride was given in large amounts. Desoxycorticosterone acetate and cortical extract (Upjohn's) were given in large doses, resulting in a lowering of the potassium level and an increase in the sodium level; 5.0 mg. desoxycorticosterone acetate, and 6 c.c. of adrenal cortex were given daily. Following this medication, the child returned to the farm and resumed his normal duties. Medication was eventually changed to 5.0 mg. desoxycorticosterone acetate in propylene glycol, given sublingually two times a day, and the patient was doing very well on this dosage at the time of their report. Since there was no clinical evidence of tuberculosis or tumor, the diagnosis of primary atrophy of the adrenal gland was made.

In 1943, Rosin and Friedman[65] described a case in a boy, 7 years of age, admitted to the hospital with symptoms of sleeplessness for a period of four days. The parents had noted that the skin was becoming darker in color about two or three months before; this was followed by marked enuresis, weight loss, and excessive fatigue upon minor exertion. A few days before entry, the child started to vomit, became more listless and gradually stuporous. The past history may be significant. There was severe pneumonia at 2 years of age, associated with very high fever of five to six weeks' duration. Between the ages of 5 and 6 years, the child had chickenpox, measles, and whooping cough, each accompanied by very high fever of many weeks' duration. The patient had enuresis "all of his life," but this was much exaggerated the last few months. The early developmental history was negative. The father and mother were living and well, and two siblings aged 9 and 6 years, were in excellent health. Physical examination revealed the patient to be dehydrated and stuporous. There was a generalized brownish pigmentation of the skin and the mucous membranes, the latter presenting a purple-brown color. Wassermann and tuberculin tests were negative. The blood chlorides were 436 mg. per cent; sodium, 320 mg. per cent; and potassium, 32 mg. per cent. The basal metabolic rate was –27 and the glucose tolerance test showed: fasting, 80 mg. per cent; 1 hour, lost; 2 hours, 100 mg. per cent; 3 hours, 103 mg. per cent; 4 hours, 100 mg. per cent; and 5 hours, 69 mg. per cent. X-rays of chest, abdomen, and skull were all negative. A very decided improvement followed the administration of adrenal cortical extract and intravenous glucose and salt solution. When the therapy was discontinued, relapses occurred. One week following therapy, the blood chlorides were 528 mg. per cent; sodium, 314 mg. per cent; potassium, 28 mg. per cent; and nonprotein nitrogen, 33 mg. per cent. The patient was given 5.0 mg. desoxycorticosterone acetate daily, but received this for only three days, because he was moved out of town. No follow-up reports were given. A diagnosis of atrophy was made because of the history of repeated severe infections in early childhood and the failure to prove that the child had any evidence of tuberculosis or adrenal tumor.

In 1946, Jaudon[66] presented a case of a 3-year-old girl, who suddenly became ill at 4½ months of age, with high fever, cough, and a generalized maculopapular rash. These symptoms disappeared in a few days, but two weeks later she developed anorexia, became listless and intermittently drowsy, began to vomit projectily once or twice a day, developed diarrhea, and lost weight.

Her previously very fair skin was noticed to be darker in color. She entered the hospital at 6½ months of age, was markedly dehydrated, and chronically ill; there was a faint generalized "tan-like" discoloration of the skin. The serum carbon dioxide combining power was 42 volumes per cent and nonprotein nitrogen, 80.5 mg. per cent. Parenteral therapy was followed by such a dramatic improvement that the patient was almost discharged. However, after twenty-four hours had elapsed without subcutaneous or intravenous fluids, she again refused food, became listless and dehydrated. The Wassermann was negative. An intradermal tuberculin test was markedly positive, almost to the point of ulceration. It was discovered that the Negro house-man had a diffuse "honeycomb" destruction of the left lung, caused by active tuberculosis from which he later expired. The possibility of Addison's disease was considered and 2.0 mg. desoxycorticosterone acetate were injected daily. Two days later, the serum chlorides were 520 mg. per cent; sodium, 300 mg. per cent; potassium, 28.6 mg. per cent; nonprotein nitrogen, 64 mg. per cent; and serum carbon dioxide combining power, 49 volumes per cent. Twenty days later the patient appeared normal in every respect, and the skin was slightly less pigmented. At this time the nonprotein nitrogen was 40.5 mg. per cent; serum chloride, 630 mg. per cent; sodium, 332 mg. per cent; and potassium, 21.1 mg. per cent. The fasting and post-prandial blood sugar determinations ranged between 20 to 50 mg. per cent but were not accompanied by symptoms of hypoglycemia. After a few days on desoxycorticosterone acetate, the appetite improved remarkably and the blood sugar level returned to normal. Pyelogram and urine examinations were essentially negative. The patient was given a high vitamin low potassium diet, and 2.0 Gm. of additional sodium chloride and 1.5 to 2.0 Gm. desoxycorticosterone acetate daily. The case has been followed for over two years. The growth and development have been normal and general health has been excellent. There has been a progressive increase in pigmentation of the skin and mucous membranes to almost "Negro" black over the exposed surfaces. Omitting the extract for twenty-four hours resulted in an immediate decrease in appetite and weight. No symptoms of hypoglycemia have developed. There was no real evidence of a tuberculous infection of other than the adrenals to account for the markedly positive tuberculin reaction. It was thought that this test was sufficiently significant in an infant 6 months of age to make the possibility of tuberculous destruction of the adrenals likely. The absence of abnormal sexual development and the failure to find an adrenal tumor supported this diagnosis. The possibility of a nontuberculous atrophy of the adrenals, associated with a tuberculous infection in some other part of the body, has not been entirely ruled out.

The following is a summary of the cases classified as *probable:*

Atkinson[67] mentioned that the first case in a child was published by Hutchinson and Startin in 1855.[68] This was a boy, aged 12 years, who had symptoms and signs of Addison's disease for a period of four months prior to death. About one year previously, he developed multiple abscesses of the jaw, back, and neck, and had a hacking cough from which he had not completely recovered when the skin pigmentation was first noted. There was "copper Indian" color of the skin. There was no autopsy.

In 1874, Caslodi[69] described a 15-year-old girl, ill for one year with asthenia, digestive upsets, and pigmentation of the skin and mucous membranes. She showed improvement but was lost sight of.

In 1886, Belaieff[70] was one of the first to oppose the prevalent view that Addison's disease was caused exclusively by tuberculosis of the suprarenal capsules. He presented the following case which had been quoted by Atkinson as the youngest child reported with Addison's disease. "A male child, apparently

7 days old, was found in the street. The integuments were slightly yellowish, with a gray tint. Later, the yellowish discolorations disappeared, and the skin gradually assumed a dirty gray color, most intense on the back and belly, and especially about the navel. Notwithstanding a good appetite, the child gradually became very weak and emaciated and died 53 days after admission to the hospital, having become unconscious during a paroxysm of tonic and clonic convulsions.'' There was no fever. The autopsy showed that both suprarenal capsules were considerably enlarged, measuring 1 inch by ¾ inch, their upper two-thirds being transformed into an aggregate of thin-walled, semi-transparent cysts, varying in size from a pinhead to a small cherry. Their content was a clear, serous fluid.

In 1889, Pottier[71] presented an 11-year-old girl having typical signs and symptoms of Addison's disease. This child eventually expired, but no autopsy was performed.

In 1894, Goulon[72] described the case of a 6-year-old girl with active rheumatic fever and chorea. While under treatment, she developed anorexia, marked fatigue, and generalized ''bronzing'' of the skin. The patient was lost sight of.

In 1897, Comby[73] described a case of a boy, aged 14 years. He had an illness of a few days' duration with signs and symptoms suggestive of Addison's disease, including generalized pigmentation. The distribution of this pigmentation, which gradually increased in severity, was highly suggestive of this disease. Comby reported definite improvement with the use of sheep's adrenal gland extract, but unfortunately the patient was lost sight of.

In 1897, Variot[74] reported a case in a girl, aged 14 years, with signs quite characteristic of Addison's disease. Injections of an adrenal extract were given for a time and the intestinal symptoms disappeared and the pigmentation definitely diminished. This case was not followed.

In 1898, Variot[75] (quoted by Dezirot) described a 14-year-old boy with weakness, ''chocolate'' discoloration of the skin, and poor muscular strength. Improvement was noted when sheep's adrenal gland was given orally. The patient was lost sight of.

In 1899, Maisch[76] presented a case of a 12-year-old boy, with all the classical signs and symptoms of Addison's disease, without clinical evidence of tuberculosis. Unfortunately, this patient was lost sight of. Maisch also described two male infants, 9 and 7 months of age, with generalized pigmentation of the skin, who presented alternating periods of diarrhea and constipation resulting in asthenia and death. Post-mortem examination failed to reveal anything abnormal in the adrenals.

In 1900, Fleming and Miller[77] reported what appeared to be Addison's disease in a 28-year-old mother and her four children. The mother had signs and symptoms, suggestive of Addison's disease, which dated from her first pregnancy seven years previously and gradually progressed. The first child, a girl aged 7 years, had had excessive pigmentation for four years, associated with headaches, stomach ache, and diarrhea. The second girl, aged 4 years, developed dark skin one year before, following an attack of eczema. She was also subject to diarrhea and vomiting. Their brother, aged 3 years, had always been a dark-skinned child. There were dark spots scattered all over his body, which had begun to appear only six months before. This boy, too, had gastrointestinal disturbances of an unexplained nature. The youngest child was a girl, 2 years of age, who had previously been of very fair complexion. But she had become distinctly darker over a period of four to five months. Diarrhea was occasionally noted. Unfortunately, there has been no follow-up of these cases. They were all living at the time of the report.

In 1907, Felderbaum and Fruchthandler[78] described a girl, 12 years of age, whose maternal grandmother and mother had died of tuberculosis. The child

had a generalized pigmentation of the skin and other symptoms quite suggestive of Addison's disease. The patient was chronically ill for a number of months and expired following a convulsion lasting eight hours. It was stated that the intestinal contents "contained large number of oval egg bodies." No autopsy was performed.

In 1907, Chemin[79] reported a case of a girl, aged 13 years, who for a year previously had been gradually going downhill with recurrent bouts of diarrhea and abdominal pain associated with a generalized pigmentation of the skin. The child had a moderate, secondary anemia. She was given an extract of adrenal gland daily, resulting in definite improvement. The author stated that the child was alive, but there has been no follow-up since that time.

In 1912, Gallais[80] reported an adenogenital syndrome in a girl who showed definite evidence of muscular weakness and generalized pigmentation. Therapy was not instituted and no follow-up reports have appeared.

In 1920, Orel[81] described a child, a brother of the patient presented by von Priesel.[82] This patient had typical macrogenitosomia and symptoms suggestive of chronic adrenal insufficiency, including the typical pigmentation. The child suddenly expired following a generalized convulsion. Unfortunately, no autopsy was obtained.

In 1921, Figenschau and Berner[83] reported a 4½-year-old girl who had been chronically ill with marked malnutrition and asthenia, had generalized pigmentation, and died suddenly following a period of coma. The left adrenal gland was completely occupied by a neuroganglioma. The right adrenal gland was apparently normal.

In 1932, Rossi[84] gave a detailed description of the symptomatology of this disease in children. He presented a case of a boy, aged 6 months, whose natural father was actually the grandfather of the child. The patient was full-term and apparently normal until 6 months of age, when an arrest in growth was noticed. Following this there were symptoms of diarrhea, weight loss, loss of vivacity, and the gradual appearance of a dehydrated and bronze-colored skin. These symptoms finally terminated in marked asthenia, fever, and continuous somnolence. Physical examination revealed marked rickets and a brownish tinge of the eyelids, neck, axillary region, backs of hands, feet, and around the genitalia. There was no evidence of sexual precocity and the cutaneous tuberculin reaction was negative. His death at 11 months of age, was preceded by sudden high fever, cough, and dyspnea. The post-mortem findings revealed bronchial pneumonia at the bases of both lungs, fatty degeneration of the myocardium, slight enlargement of the liver and spleen, and complete absence of the right kidney, corresponding ureter and renal vessels. There was enlargement of the left kidney and increase in its consistency, and the cut surface showed a grayish color. The adrenal gland on the right was in normal position, somewhat reduced in size and the consistency increased. Histologic examination showed nothing particularly abnormal in regard to the cortex, but the medullary tissue was completely absent over a large portion of the gland, and in its place there was only a scarce chromaffin cell. The left adrenal gland was in the normal location and histologic alterations were similar to that noted. The author states that the age, history, and absence of any signs of an inflammatory process, point to this being a congenital lesion.

In 1936, Namiki and Nitto[85] reported a 10-month-old girl with signs and symptoms suggestive of Addison's disease. Death was sudden, but no autopsy was performed.

In 1936, Harnapp[86] presented a boy, aged 12 years, with pigmentation of the skin of three years' duration. Complaints of intestinal upsets and headaches were noted. The patient responded to treatment with cortical extracts,

common salt, and ascorbic acid. Exacerbations of these symptoms continued despite therapy. The serum chlorides ranged from 364 to 387 mg. per cent; the sodium, 238 to 260 mg. per cent; and potassium, from 17.7 to 18.8 mg. per cent. Dextrose, galactose, fructose, and adrenalin tolerances were done. The tuberculin and Wassermann tests were negative. The child was alive at the time of presentation, but there have been no follow-up reports.

In 1936, Kagan and Holeberg[87] described a case of a boy, 11 years of age, who entered the hospital in a state of collapse, responding promptly to the administration of salt solution in large doses. The child suddenly became worse when discharged from the hospital but again improved when 6.0 Gm. of sodium chloride were put in his milk daily. There were no reports on the blood chemistry, adrenal extract was not used, and there has been no follow-up.

In 1937, Borghini[88] presented a 13-year-old Italian boy who had been delicate all of his life. He was a thin, undernourished boy, subject to attacks of weakness upon slight effort. The skin was uniformly pigmented. His mother died of typical Addison's disease; however, this pigment was followed for five years with no noteworthy change in his condition. No statement was made as to therapy and there have been no follow-up reports.

In 1940, Casaubon and Cossoy[89] described a 12-year-old girl whose skin became pigmented, and who presented symptoms of one year's duration suggestive of Addison's disease. The tuberculin and Wassermann tests were negative. The serum sodium was 335 mg. per cent. Despite the administration of cortical extract and adrenalin, the patient had a generalized convulsion and expired. No autopsy was performed.

The following cases are thought not to be Addison's disease, and are classified as *doubtful:*

In 1863, Steffen[90] presented a 7-day-old girl, without signs or symptoms of Addison's disease. The patient expired two months after an operation for harelip. At autopsy very large hemorrhagic adrenals were found.

In 1865, Pitman[91] described a 3-year-old girl as a case of Addison's disease. There was generalized hirsutism with no increased pigmentation of the skin. The child expired following an attack of continuous vomiting. The right adrenal was normal, but the left was destroyed and replaced by a very large medullary cancer, weighing 2 pounds, 5 ounces. The liver was also cancerous.

In 1866, Faure[92] described a case of a 13-year-old boy with extensive tuberculosis involving the vertebrae and causing much destruction of other bones. The patient did present symptoms of Addison's disease, but there was no generalized pigmentation of the skin. At autopsy the left adrenal gland was found to be normal and the right adrenal was enlarged, containing a few miliary tubercles. The lungs, mesenteric glands, and intestines were normal. However, there was extensive tuberculosis involving the bones. Presence of one normal adrenal gland, only slight involvement of the other, and extensive tuberculosis elsewhere make it seem unlikely that the symptoms of this patient were due to chronic adrenal insufficiency.

In 1879, Goodhardt[93] described the case of a 5-year-old child who suddenly expired. There were no symptoms or clinical findings suggestive of Addison's disease. No detailed history or report of the physical findings was given. At post-mortem, tubercles were found in the cerebellum and pons, and one tubercle in one adrenal gland.

In 1895, Zinnis[94] presented the history of a 3-year-old boy with chronic diarrhea, anemia, and bronzed skin. The child supposedly recovered after treatment with iron and a proper diet.

In 1899, Maisch[76] reported a 9-month-old boy who presented generalized pigmentation, periods of constipation, diarrhea, and weight loss. At autopsy

there was a generalized increase in melanin pigment in all the viscera without any pathologic evidence to account for the patient's death. The adrenals were said to have been normal.

In 1903, Richon[95] published a case of a 10-year-old girl, whose father died of pulmonary tuberculosis. She became very weak, lost her appetite. The mother stated her skin had always been dark, but it became more marked on the face, trunk, and groin during the last few weeks. The patient improved with injections of adrenal extract. But three months after the onset of treatment she expired, following an episode of abdominal pain, vomiting, and diarrhea. Post-mortem revealed pulmonary and intestinal tuberculosis but the adrenals were healthy in appearance.

In 1905, Nobecourt[96] described a case of an 18-month-old boy whose mother had active pulmonary tuberculosis. The child was found to be emaciated, with generalized pigmentation of the skin and mucous membranes. He also presented signs of tuberculous meningitis immediately before death. At autopsy there was evidence of generalized tuberculosis, involving the mediastinal and mesenteric glands, lungs, and spleen. However, the adrenals were normal.

In 1916, Rutelli[97] presented a 10-year-old boy, who had "brown" skin for six years and a tubercle on one finger. After adrenal extracts were taken, the blood pressure rose from 65 to 82 mm. There was very slight asthenia and no weight loss. No other details were reported.

In 1917, Hertz, Secher, and Pittman[98] reported the progress of a male patient from 2 to 16 months of age. The child had marked secondary anemia and symptoms of Addison's disease, but no mention is made of pigmentation. At autopsy there was a neuroblastoma of the left adrenal, but the right adrenal gland was normal. The author mentions this case as proof that Addison's disease can occur without the presence of tuberculosis. There were no blood chemistry changes reported.

In 1922, Cannata[99] described a case of a 16-month-old boy who had symptoms and signs of Addison's disease, including pigmentation. There was spontaneous improvement and there have been no further reports.

In 1927, Morabito[100] presented cases of a brother and sister 7 and 10 years of age, respectively. Each had signs suggestive of Addison's disease. The Wassermann tests were positive. No further details were given. There have been no follow-up reports. It is interesting to note, however, that rare cases thought to have been due to syphilis, have been reported in adults. With institution of antisyphilitic therapy these have improved promptly.

In 1927, Peutz[101] published a case of a 12-year-old boy who was doing poorly because of generalized weakness, weight loss, and a secondary anemia. Two members of the boy's immediate family died of tuberculosis. This child, however, was doing well at the time of publication and there has been no further report.

In 1931, Von Priesel[82] presented a case of a 5-year-old girl with pseudohermaphroditism, secondary to adrenal hyperplasia. He noted that there was generalized pigmentation of the skin, but no other symptoms and signs of Addison's disease. There was no follow-up.

DISCUSSION

In addition to destruction of the adrenals by tuberculosis, neoplasms, and atrophy, the recent literature[59, 61, 63] has demonstrated that hypofunction of the adrenal cortex, resulting in symptoms of Addison's disease, may be secondary to hyperplasia of the androgenic zone.

In 1940, Dijkhuizen and Behr[102] described a 2-week-old male infant with pseudohermaphroditism, who became ill following vomiting, dehydration, and diarrhea. A diagnosis of intestinal obstruction was made, but operation failed

to reveal the cause. No autopsy was obtained. Later, the brother of this child was hospitalized at 2 months of age, because of episodes of violent vomiting and diarrhea. A diagnosis of intestinal obstruction was again considered. Autopsy showed both adrenals to be very large, presenting marked gyrations and grooves. Together they weighed 22.0 grams.

Through the courtesy of Professor Pelanze of Amsterdam, these authors[102] presented the third case, a boy, who began to vomit and had loose stools shortly after birth. Post-mortem revealed a large thymus and very large adrenals, weighing 12.0 grams each, the same size as the kidneys.

Their fourth case, a 5-week-old girl, had been vomiting constantly for ten days, had diarrhea for five days, became markedly emaciated, and expired at 3½ months of age. Autopsy revealed only very large hyperplastic adrenals, together weighing 34.0 grams.

Even though Dijkhuizen and Behr's four cases were reported as deaths secondary to hyperfunction of the adrenal cortex, it was thought that they more probably represented instances of severe cortical insufficiency, caused by marked hyperplasia of the androgenic zone. Unfortunately, no notation was made about the color of the skin. No chemical determinations were made of the blood, nor was a definite statement made about the genitals, except in the one case of a pseudohermaphrodite. The sizes of the prostates and testes were not recorded.

The case of Wilkins, Fleischmann, and Howard[61] unquestionably demonstrated that the androgenic tissue could become so hyperplastic as to cause destruction of practically all of the normal cortical tissue.

Grollman[103] states: "The symptoms of Addison's disease associated with adrenal virilism are caused by the encroachment of the androgenic zone on the true cortical tissue." If the male patients described by Dijkhuizen and Behr did not show enlarged genitals before death, they might have shown these signs had they lived longer. Wilkins' patient did not show enlargement of the penis until past 3 months of age.

Dijkhuizen and Behr[102] also reviewed the literature and found six additional cases in patients varying from 5 weeks to 3½ months of age. Two of these were pseudohermaphrodites. One newborn female in addition to hyperplasia of the adrenals had a uterus the size of a 5-year-old girl, but the ovaries were normal. All of these patients expired following intestinal upsets. No further details were given.

Even at the present time, it is difficult to differentiate accurately between the hyperplastic androgenic fetal zone and the true cortex, nevertheless there is sufficient similarity between these and the so-called *proved* cases to warrant their classification as *probable*. These cases have not been included, however, since they were not reported as adrenal insufficiency or Addison's disease.

A great deal of consideration was given the case presented by Belaieff,[70] since this 7-day-old infant was quoted by Atkinson[67] as the youngest child reported with Addison's disease. The terminal symptoms, generalized convulsions, and the presence of numerous cysts comprising the upper two-thirds of the adrenals suggested cortical insufficiency as the cause of death. The fact that no histologic evidence of absent or decreased cortical tissue or other post-mortem findings was given, and the absence of true bronzing of the skin, prompted the classification of this case as *probable*.

The cases of Hertz, Secher, and Pittman,[98] with destruction of one adrenal gland by tumors were classified doubtful because of the absence of pigmentation and the finding of one normal adrenal. There were three proved cases of unilateral tuberculous involvement of the adrenals; however, all these cases, in addition to presenting typical symptoms, also showed generalized pigmentation.

The third case, presented by Figenschau and Berner,[83] of complete destruction of one adrenal gland by a neuroganglioma was placed in the *probable* category because of the classical symptoms and pigmentation.

Blood chemical changes and the response to potent extracts are probably the most reliable criteria for use in properly classifying this type of case.

It is felt that reasons for the classification of the other cases require no further explanation.

SUMMARY

One hundred cases of children, below the age of 15 years, have been reported in the literature before June, 1945, with the diagnosis of Addison's disease.

Sixty-two have been classified as *proved*, twenty-three as *probable*, and fifteen as *doubtful*.

The following summary has been made of the *proved* cases:

Age Incidence.—The onset of symptoms was first noticed in children:

Under 2 yr. of age in three, or 4.9 per cent
From 2 to 5 yr. of age in three, or 4.9 per cent
From 5 to 10 yr. of age in seven, or 11.5 per cent
From 10 to 15 yr. of age in forty-eight, or 78.7 per cent
The age was not reported in one case

Sex and Race Incidence.—Thirty-eight, or 61.3 per cent, were males and twenty-four or 38.6 per cent were females, giving an almost 2 to 1 incidence in favor of the males. This ratio is in agreement with that usually quoted in adults with tuberculosis of the adrenals. It is frequently stated, however, that the ratio is reversed in primary atrophy in adult patients. It is, therefore, of interest to note that the children with atrophy of the adrenals were all males. To my knowledge, no cases have been reported in the Negro race.

Symptoms and Signs.—Fifty-three, or 85.5 per cent, of the cases manifested gastrointestinal symptoms some time during the course of the illness. No statement was made concerning the presence or absence of intestinal complaints in the remaining nine, or 14.5 per cent. The incidence of gastrointestinal symptoms, therefore, is probably much higher than that stated. Attacks of vomiting, diarrhea, and generalized abdominal discomfort were the most common complaints. Asthenia, anorexia, weight loss, dehydration, and general debility were present in practically all of the cases. In eight, or 12.9 per cent, there were repeated convulsions which might be interpreted as hypoglycemic in origin.

A definite statement was made concerning the color of the skin in sixty patients. Of these, fifty-six, or 93.3 per cent, had a generalized pigmentation.

The duration of symptoms before death ranged from three days to four years. No definite statement was made in seventeen, or 27.4 per cent, of the cases. Of the remaining forty-five, in twenty-five, or 55.6 per cent, death occurred seven months or less after the onset of symptoms. Twenty, or 44.4 per cent, of the patients were ill for one year or longer.

Mode of Termination.—By far the majority of these children presented the picture of a progressive debilitating illness, resulting in the usual slow death. However, twenty, or 32.2 per cent, of them exhibited dramatic episodes of convulsions, profuse diarrhea or vomiting, or sudden coma just prior to death.

Etiology.—In one case the nature of the pathologic involvement of the adrenals was not given. Of the remaining sixty-one, fifty-three, or 86.9 per cent, were of tuberculous origin, fifty, or 94.3 per cent, showed bilateral involvement of the adrenals. Pulmonary tuberculosis was present in twenty-three, or 43.4 per cent, and tuberculosis of the mesenteric glands was present in seven,

or 15.0 per cent, of the cases showing tuberculous adrenals. In five, or 8.0 per cent, of the cases there was atrophy of both adrenal glands without clinical or pathologic evidence of tuberculosis. In three, or 4.8 per cent, macrogenitosomia was an associated finding. Of the six cases, in which the patients were alive at the time of the report, two were diagnosed atrophy; two, hyperplasia; and two, tuberculosis of the adrenals.

In adults, pyogenic abscesses, vascular lesions, amyloid degeneration, mycosis fungoide and echinococcus cysts have been responsible for destruction of the adrenal glands resulting in the development of Addison's disease. To my knowledge, these etiological agents have not been responsible for this disease in children.

Treatment.—Although in the older literature there was an occasional reference to the use of crude adrenal extracts, it was not until 1927 that Hartman and associates[104] demonstrated that Interrenalin prolonged the lives of adrenalectomized dogs. The period between 1936 and 1941[105-110] produced important contributions in the isolation of various fractions of the whole gland which put potent extracts at the disposal of the clinician. For these reasons, and the lack of knowledge until 1932[4] concerning the importance of electrolyte metabolism, these patients could not have received adequate therapy until after this time.

In Butler, Ross, and Talbot's case,[59] associated with macrogenitosomia, there was sudden collapse on restriction of fluids or sodium chloride but the patient was apparently well-regulated on the addition of 2 to 3 Gm. of sodium chloride to the diet, without the use of extracts.

Ginandes' patient,[62] although probably having tuberculous adrenals, was well-adjusted on daily injections of whole cortical extract. In addition, a diet high in sodium-chloride and low in potassium was prescribed. During the acute phase of the illness a dramatic response was obtained with normal saline and glucose intravenously.

In the other case associated with macrogenitosomia the patient was regulated by substituting physiologic sodium chloride solution for water in the formula and the addition of 0.2 c.c. desoxycorticosterone acetate by injection daily. At 9 months of age the therapy was changed to 3 drops of desoxycorticosterone in propylene glycol, five to six times daily sublingually.

Anderson's[64] 11-year-old patient with probable atrophy of the adrenals was given 5.0 mg. desoxycorticosterone acetate and 6.0 c.c. whole gland extract daily, by injection. The therapy was later changed to 5.0 mg. desoxycorticosterone in propylene glycol twice daily sublingually.

Rosin and Friedman's patient,[65] a case of adrenal atrophy, was improving on injections of desoxycorticosterone, but he was lost sight of.

Jaudon's patient,[66] a probable case of tuberculosis of the adrenals, has been well controlled for over two years by injections of 1.5 to 2.0 mg. desoxycorticosterone acetate daily. Recently, four 125 mg. desoxycorticosterone acetate pellets were implanted and daily injections are no longer necessary. The child has remained in good health.

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The Academy Study of Child Health Services

REPORT ON ACADEMY STUDY

Under title of The Social Aspects of Medicine in the March issue of the JOURNAL, Dr. Park has thrown an aura of suspicion over the true parentage of the Academy's war baby—now more respectfully known as "The Study of Child Health Services." Partly in order to forestall the appointment of "another committee to investigate," although there is nothing to hide, those of us concerned with rearing this child wish to clarify for Dr. Park and his readers "this mysterious affair." More particularly, however, we are eager to describe the extent to which many friends of the Academy have supported this infant prodigy and have once more demonstrated their faith in the activities of the Academy.

Relationship of the United States Public Health Service and Children's Bureau.—It is apparent that there still exists considerable doubt and misgiving arising from the fact that the United States Public Health Service and the Children's Bureau have been asked to assist in the organization and conduct of this Study. This action was taken in accordance with a recommendation presented to the Academy membership at its annual meeting in November, 1944: "That the American Academy of Pediatrics requests the United States Public Health Service and Children's Bureau to undertake with the Academy a survey in every state to determine . . . information concerning the present situation and extension of personnel and facilities needed in each state to meet the objectives as stated." Those who wish to refer to the full report will find it published in the JOURNAL (J. Pediat. **25:** 625, December, 1944). This recommendation having been unanimously approved in open meeting, it naturally followed that Dr. Parran and Dr. Martha Eliot were asked to cooperate with the Academy in this Study. Both responded with wholehearted support, contributing the full-time services of expert medical and statistical personnel and equipment. Cooperative planning was begun and at the same time it was made clear that the control of the project was to remain in the hands of the Academy. Thus there has been established an effective and happy working relationship wherein the authority of the Academy has at no time been questioned.

In view of the desirability of working in close proximity to the two cooperating government agencies, a Central Office was set up in Washington to serve as headquarters for the Director and Executive Staff. Washington was chosen for the Central Office with some hesitation since this location might be interpreted by some as indicating that the Study is a government project. It very definitely is not a government project. The Director is paid by and answerable to the Academy of Pediatrics; the personnel who are on loan from the government agencies are under his direction. The responsibility for the success of the undertaking belongs to the Academy.

Instead of viewing with suspicion and misgiving the intentions of those who recommended this cooperation they should be commended for a step without which the Academy would now find itself in an embarrassing plight. It is fair to state that these planners wrought better than they knew. No one at the outset appreciated the enormous mass of statistical data to be collected or the labor involved in adequate analyses. The Academy does not have at its disposal the necessary statistical facilities or in fact the personnel or experience to undertake a task of such broad scope. Even we at the Central Office appreciate that we do not yet fully visualize all that is involved in drawing together, coding, and tabulating information from all hospitals, medical schools, health services, and physicians throughout the country.

.Questions have also been raised with regard to who is to interpret the information and the purpose to which the results of the Study will be put. The function of the Study as it is now organized is to obtain factual material. Much confusion will be avoided if it is kept clearly in mind that this Study is to be considered only as the first step toward the attainment of the Academy's objective which, briefly stated, is to make available throughout the country improved and more evenly distributed medical care for children. At the close of the Study the material will be presented in a report which will be available to all who care to use it. This report will be limited to a presentation of factual data and will not include broad interpretations or recommendations. A program of action resulting from this report will be a responsibility of the Academy at a later date. Only after the facts are known can a fair estimate be made of the interpretations and opinions that may arise from them. In addition to publishing an over-all report, information gathered through the State Programs now under way will be returned to State chairmen of the Academy in tabular form broken down to State, County, or Metropolitan levels. It is hoped thereby to stimulate local groups to evaluate the services within their own communities as a basis for local planning.

The responsibility for collecting and reporting the desired information and also the relationship between the American Academy of Pediatrics, the United States Public Health Service and the Children's Bureau have been repeatedly described at many meetings of the Academy. However, there are many who have been unable to attend these meetings and have not had the opportunity to become fully informed, of whom some still seem to be suspicious of the motives of the government agencies, particularly the Children's Bureau. So again in order to allay any lingering misgivings it is worth reiterating that there is no intention on the part of anyone to use this Study for any dire motive. If, after the facts are gathered and the Academy has drawn up a program based upon them, there are those who wish to oppose that program—and it is hard to believe that such will not be the case—then pediatricians themselves will be able to support their cause by a background of factual data which is now lacking.

National Foundation for Infantile Paralysis.—When the Study was first undertaken not only was its scope underestimated but also its cost. At the outset the Academy appropriated $8,000 from its reserve fund. More recently it has added another $10,000 to its appropriation which altogether represents a large proportion of its total reserve fund. This is clear evidence of the earnestness with which the Academy is meeting its own commitment. But even so this is a relatively small proportion of the total expense. It was apparent that grants of major proportions would be needed to help the Academy in this project.

The National Foundation for Infantile Paralysis was one of the first sources to which the Academy looked for help. This Foundation is particularly concerned with improving the resources for one aspect of pediatric care and showed immediate interest in the Academy's Study. After a detailed examination of the proposed plan the Foundation has made a grant of $116,000 for a two-year period. It is intended that this grant should cover the expenses involved in maintaining the large staff for which the Academy is responsible in the Central Office, salaries and expenses of Regional Directors, cost of preparing and printing questionnaire schedules and publicity material, and general operating expenses of the Central Office. This grant, although generous, is not expected to take care of the cost of State programs throughout the country. However, at the State level the National Foundation for Infantile Paralysis has again come to our support. A memorandum has been sent from the National Headquarters of the Foundation to all their field representatives urging them to encourage County Chapters to give not only moral support but also financial assistance to State programs when asked to do so by the State Chairmen of the Academy. Whether or not financial support is obtained at the State level from the National Foundation it is considered desirable from the point of view of the mutual interests of the Foundation and the Academy that their field representatives and other persons interested in the

County Chapter activities should cooperate in accepting appointments to the Academy State Advisory Committees. The Central Office of the Study has already received word from many States demonstrating the willingness of the Foundation to offer generous support to State chairmen.

Further Financial Support.—In order to stand on as broad a basis as possible in financing this major effort, the Academy has sought support from several of the larger Foundations and also from several of the commercial firms which have special pediatric interest. The Kellogg Foundation has expressed its approval of the Study and has offered to appoint one or more of its trained field workers to assist in the collection of data. A letter has recently been received from the Executive Vice-President of the Field Foundation stating that the Directors of this Foundation have voted a contribution, the amount of which has not yet been specified. The services of the Executive Director of the New York State Study have been contributed by the Metropolitan Life Insurance Company.

Generous support has been received from Mead Johnson and Company, M and R Dietetic Laboratories, Carnation Company, the Pet Milk Company. Lederle Laboratories, Inc., has also stated that they would make a contribution which has not yet been received.

In addition to these grants received by the Central Office, State Chairmen who are responsible for financing State Programs from within each State have received financial contributions from many different sources. So far it appears evident that they have been able to do so without undue difficulty. Support at the State level from the National Foundation for Infantile Paralysis has already been described. In many cases the State Health Department has met part or all of the expenses of the State program by funds available under Title V of the Social Security Act. A few States have sought and received grants from local Foundations. In certain areas contributions have been requested of the pediatricians themselves.

The American Academy of Pediatrics is indeed fortunate in the number of friends who may always be counted upon to come forward and assist its activities. The happy relationships which this Study is promoting throughout the country are well demonstrated by the following quotation from a recent letter of Dr. Theodore E. Allen, Executive Secretary for the Metropolitan New York area: "The response to our never ending letters asking for sponsorship for this Study has continued to be a very happy one. It is a pleasure to open the mail in the morning and see in how many different ways agencies and individuals can say they are pleased to help our project."

JOHN P. HUBBARD, M.D.

The Social Aspects of Medicine

THE BRITISH HEALTH BILL

3rd April, 1946

Dear Dr. Park,

You asked me to secure some views on our new Health Bill, especially if I could persuade people completely opposed and completely in favour to state their case, with a summing up of the moderate view. But it is first necessary to make it clear that with certain few exceptions the medical profession is all "moderate." What I mean is that for a quarter of a century we have all been urging a complete health service and most of what is really good in the present proposals has come from the profession. So that in principle we welcome the bill, although there are many points of detail that require careful consideration and above all we all want to see professional freedom left entirely unfettered. Moreover, the present proposals seem to us to concede much that we have asked for since the original "White Paper" on "A Comprehensive Health Service" was issued by the Coalition Government in February, 1944. There may be—and we hope there will be—still more conceded in the course of the bill's passage through Parliament, and therefore what I am writing may to some extent be out of date before these lines appear. Another important point is that many matters of detail are left to be dealt with in Regulations and in this respect there is as yet no clear picture, for example, of a Child Health Service, on a national scale. But the bill will go through, and root and branch opposition will get us nowhere. The Government has a huge majority. What we must fight for is to get what we think are improvements.

First I will try and summarize very briefly what the bill intends to do. Clause I of the printed bill states the whole issue clearly:

> "It shall be the duty of the Minister of Health to promote the establishment in England and Wales* of a comprehensive health service designed to secure improvement in the physical and mental health of the people of England and Wales and the prevention, diagnosis and treatment of illness, and for that purpose to provide or secure the effective provision of services in accordance with the following provisions of this Act. The services so provided shall be free of charge, except where any provision of this Act expressly provides for the making and recovery of charges."

Broadly the provisions proposed fall into three groups. First comes the hospital and special service. The Minister is to take over all hospitals (including mental hospitals)—voluntarily supported or run by local authorities (county councils and borough councils) out of rates. The "Teaching Hospitals" are excepted from this transfer of ownership; that is, those with undergraduates and in some limited instances post-graduate medical schools, although they will have reconstituted governing bodies and have to come into the general plan for hospital services. All such services are to be administered by Regional Hospital Boards, probably about 16 to 20, based upon a university area and with provision for membership by university representatives, the medical profession, the local health authorities of the area and others concerned. These boards will delegate the running of the hospitals to local Hospital Management Committees with small house committees for individual hospitals if required. Specialists will work, so to speak, at and from the hospitals, but no details are available on how they will work, especially as regards domiciliary consultations. It is provided that the Regional Boards shall be given as much financial freedom as possible, by a system of block annual budgets or otherwise.

Next comes the provision of Health Centres and all general practitioner services. The Centres will be provided and equipped by the local authorities (county and borough councils),

*Scotland will be dealt with in a separate bill.

but the doctors will work under a new body—the Local Executive Councils with half membership for local practitioners and half from the major local authorities of the area concerned. Doctors will be paid a basic salary plus capitation fees. Finally come the supplementary services to be provided for the most part by the local authorities and including child welfare, health visiting, home nursing, ambulance services and so on.

At the side of the Minister there is to be a Central Health Services Council of 41 members, of which 21 at least will be medical practitioners and the rest experts in various aspects of hospital and professional work. Some of the medical members are to be ex officio (e.g., Presidents of the Royal Colleges) and the rest appointed after consultation with professional and other bodies. The Council is to be advisory in function and will work partly through standing advisory committees.

The estimated annual total cost is put at £152 million, of which £32 million will come out of contributions to the new National Insurance Fund and about £10 million from rates levied by local authorities. The balance will be found from central funds raised by the ordinary methods of taxation.

Work among children, as already stated, has not been separately considered in detail. Hospital and specialist services will come under the new regional body; general practitioner work under the new local executive councils; child welfare and school medicine under local authorities and in this case there is some confusion because some relatively minor authorities have been allowed to retain their supervision of education under the new Education Act and the child health services will go with education.

The most obvious criticism which must now be apparent is the administrative complexity of the scheme. It would surely be better, it is argued, to put all health services under the new regional bodies, so as to avoid the chaos likely to arise when three or four authorities are dealing with an individual patient. But it will probably be answered that these regional bodies are too remote from the local government electors and not elected on a direct democratic basis. In any case, the exact composition of the new bodies is not stated in the bill and until this is known it is difficult to argue for giving them even greater power.

The transfer of hospital ownership has aroused a great outcry. The voluntary hospital spokesmen have used the phrase "mass murder," but this is the language of hyperbole and it is perhaps difficult for those who work at first class voluntary hospitals in London to realize the disadvantages under which these institutions have to exist in the country. The surveys of the hospital services of England and Wales that have been made in recent years have revealed a state of affairs which calls for radical reorganization. This is even more true of local authority hospital services outside a few enlightened areas such as those of the London County Council and Middlesex County Council.

Criticisms of the family practitioner service are mainly that the Health Centres, widely publicised, have not even reached the blueprint stage, and experimentation should precede the establishment of definite plans. The proposed control of the distribution of doctors, to be achieved in a sort of negative way, is still causing considerable concern, and this added to the abolition of the sale of practices (with compensation) is taken to mean a serious step towards a full-time state salaried service. The main professional bodies have proclaimed themselves sternly against this, and it is round this point that most criticism is likely to centre in the coming weeks. Private practice, alike for general practitioners and specialists, is to be allowed with certain safeguards, but it is freely suggested that the whole trend of the bill will be to abolish such private work in a relatively short time.

This is a brief outline of the bill and the main criticisms. If we can secure a Regional Board with adequate medical and university representation and get such a Board to take on more of the administration of the non-hospital services, then I believe we can make the new service work well for the sick of this country. But, as has been often said, it is a "medical service" rather than a "health service" as at present outlined. It will be for those who work it to give it the necessary twist to the preventive side.

ALAN MONCRIEFF, M.D., F.R.C.P.*

*Nuffield Professor of Child Health, Institute of Child Health, University of London.

News and Notes

MALIGNANT TUMORS OF INFANCY AND CHILDHOOD—ORGANIZATION OF A NEW CONSULTATION SERVICE

Announcement is made of the establishment of a consultation service to provide assistance in the diagnosis and treatment of tumors of infancy and childhood. This is a further step in the organization of a Children's Cancer Center, which is a unit of the new Medical Center for Children in Boston.

This is not a tumor registry. It is designed, rather, to give without charge, immediate diagnostic assistance and advice concerning therapy and prognosis, to any doctor who will send the necessary clinical data, microscopic sections, or x-rays. Replies will be given by air mail, or when necessary, by telephone, or telegraph. This project which is supported in part by a Grant-in-Aid from the National Advisory Cancer Council will be paralleled by a research program concerning the biology of tumors of early life, with a consideration also of the clinical, pathological, and epidemiological aspects of the problem.

The consultation service will be rendered by a group of three Pathologists, Dr. S. Burt Wolbach, Dr. Charles F. Branch, and Dr. Sidney Farber, and one Roentgenologist, Dr. Edward D. B. Neuhauser, with the cooperation, when indicated, of the entire staff of The Children's Hospital, through the Chiefs of the clinical services. Doctors representing all of the clinical and laboratory specialties concerned with the infant or child will be available for consultation.

Communications should be sent to Dr. Sidney Farber, The Children's Hospital, 300 Longwood Avenue, Boston 15, Mass., beginning Aug. 1, 1946.

FELS INSTITUTE'S PROGRAM AND FACILITIES EXPANDED

The Samuel S. Fels Fund of Philadelphia announces the erection of a new research laboratory building on the Antioch College Campus at Yellow Springs, Ohio. The new building, to cost about $400,000, exclusive of equipment, is to house the activities of the Fels Research Institute. The Institute's program, devoted to the study of growth and development of children, is being expanded considerably in the following areas: Biochemistry with emphasis on blood and urinary enzymes, vitamin adequacy, ketosteroids, estrogens, and other hormones, in relation to growth progress and behavior; Genetics with emphasis on the inheritance of biochemical and physiological function patterns and growth patterns; Physiology with emphasis on resistance level to physical or emotional stress in relation to predisposition to psychosomatic disease and personality.

To house these activities and those of the Psychology and Physical Growth sections, physiological, physical growth, biochemical, and psychological laboratories, as well as office and library space, will be provided.

A new scientific advisory board has been created, consisting of Dr. Robert Yerkes, Yale, psychobiology; Dr. Ashley Weech, Cincinnati University, pediatrics; Dr. E. V. Cowdry, Washington University, anatomy; and Dr. Maurice Visscher, University of Minnesota, physiology. The Institute, established in 1929, is under the direction of Dr. L. W. Sontag.

Dr. Alvaro Aguiar of Rio de Janeiro, Brazil, has been elected President of the Brazilian Pediatric Society for 1946 and 1947.

The Pediatrician and the War

The following members have been released from service:

Dr. M. Bernard Brahdy, Mt. Vernon, N. Y.
Dr. Burtis B. Breeze, Rochester, N. Y.
Dr. Ward L. Chadwick, Denver, Colo.
Dr. Edward J. Denenholz, Chicago, Ill.
Dr. Wilbur J. Fisher, Buffalo, N. Y.
Dr. Ellis H. Harris, Winnetka, Ill.
Dr. C. Jack Harrison, Chicago, Ill.
Dr. Robert E. Jennings, East Orange, N. J.
Dr. Daniel B. Landau, Hannibal, Mo.
Dr. Jacob J. Lichterman, Brooklyn, N. Y.
Dr. Joseph Palma, Honolulu, Hawaii
Dr. Sam Phillips, Little Rock, Ark.
Dr. John F. Sander, East Lansing, Mich.
Dr. James R. Sickler, Tucson, Ariz.

The following promotions have been reported:

Major Jack Chesney, Knoxville, Tenn., to Lieutenant Colonel
Captain W. V. B. Diering, Chicago, Ill., to Major

Book Reviews

The New-Born Infant: A Manual of Obstetrical Pediatrics. Emerson L. Stone, M.D., ed. 3, Philadelphia, 1945, Lea & Febiger, 314 pages.

In reviewing this book by Dr. Stone, it must be remembered that, because the author is not primarily interested in pediatrics, the work will not live up to some pediatric ideals on such subjects as physiology and development of the newborn and infant feeding.

It does present, however, a common sense attitude toward the problems of newly born infants, and it is felt that it should be a part of the library of anyone interested in this most precarious period of human life. The material is interestingly written, and the information, for the most part, is accurate and well documented.

In evaluating the book, it would be fair to say that it forms a sort of missing link between pediatrics and obstetrics and that any such effort is decidedly worth while. If the pediatricians could know more about obstetrical problems and obstetricians know more about pediatric problems, both of these specialties would be better off.

C. A. A.

Comment

A JOB FOR EVERY FELLOW

In last month's issue of the JOURNAL a new department was started: The Academy Study of Child Health Services. In the department this month Dr. Hubbard tells of some of the financial support the study has received. In addition to the $18,000 contributed by the Academy to start the study and the large contributions of the United States Public Health Service and of the Children's Bureau in the way of personnel, gifts of money or staff have been made by the National Infantile Paralysis Foundation, the Field Foundation, and the Kellogg Foundation. Large contributions have also been made by a number of commercial corporations who are deeply interested in the health problems of infants and children and who recognize the leadership of the Academy in such matters. The huge sum of money which the two-year study will cost is in sight. This splendid financial support would not have been received were it not for the recognition that a sound factual basis is necessary for the development of intelligent planning for child health work in the future. Quite frankly, almost everyone is more or less fed up with the emotional and at times acrimonious discussion over health plans for children which has recently been taking place. This has been due in no small part to the discussions being based on opinion, or reflecting some social or political ideology. When the facts are found and made known it should be possible to formulate plans to meet the needs which will find support from all concerned.

Money alone will not make the study of value or a success. What is of equal importance is the wholehearted support the study is being given by the medical profession and by public and private child health agencies. Many state medical societies are already sponsoring and assisting the study which is being conducted at state levels. An editorial in the May 4 number of the *Journal of the American Medical Association* appeals to the entire medical profession to support and aid the study. We will not quote from this as it has probably been read by most Fellows. In the April 26 number of *Public Health Reports* an outline of the study was published calling for its support by all public health officers. It was stated in this article that the Academy has formally requested the support and assistance of all public health officials and the following comment was made: "This request, addressed by a national medical organization of high standing to governmental agencies, represents another milestone in cooperative action." So we find rallying to the support of the study not only money but the necessary technical and professional support which the study requires. We must not forget, however, that it is an undertaking and a responsibility of the Academy of Pediatrics. From the way the study is organized its success and value, in the ultimate analysis, will depend on the work and enthusiasm of the Fellowship.

The response on the part of the fifty-odd State Chairmen who will be responsible for much of the work has been splendid. They have accepted tremendous responsibility, but they cannot do it all. It will call for time and effort on the part of every individual Fellow. The pediatricians through their Academy have assumed leadership and they must not and will not fall down on the task which is the responsibility of every individual member.

It may eventually turn out that the Academy study, by pointing the way to united efforts to provide better health and medical care for the children of the United States, will help to solve the complicated and perplexing problems of adjustment between individual effort and public and private health agencies concerned with better medical care for all.

B. S. V.

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JUN 24 1946

Vol. 28 JUNE, 1946 No. 6

THE JOURNAL OF PEDIATRICS

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